

# EXHIBIT 13



US 20120006322A1

(19) **United States**(12) **Patent Application Publication**  
**Anderson et al.**(10) **Pub. No.: US 2012/0006322 A1**(43) **Pub. Date: Jan. 12, 2012**(54) **DRUG DISPENSER**(52) **U.S. Cl. .... 128/200.23; 128/203.12**(75) **Inventors:** **Gregor John McLennan**  
**Anderson, Hertfordshire (GB);**  
**Paul Kenneth Rand, Hertfordshire**  
**(GB)**(57) **ABSTRACT**(73) **Assignee:** **Glaxo Group Limited**(21) **Appl. No.:** **12/377,416**(22) **PCT Filed:** **Aug. 21, 2007**(86) **PCT No.:** **PCT/EP2007/058676**§ 371 (c)(1),  
(2), (4) **Date:** **Sep. 29, 2011**

There is provided a drug dispenser device comprising a housing defining a first chamber; extending from said housing and defining a second open chamber, an outlet for insertion into a body cavity of a patient; provided to said first chamber of the housing, a discharge block defining a discharge block orifice; receivable within the first chamber for movement there-within, a drug discharge device, said drug discharge device having a longitudinal axis and comprising a container for storing a drug formulation to be dispensed, a discharge mechanism and a discharge channel from said container, wherein said discharge channel is receivable by said discharge block to enable discharge of said drug formulation via said discharge block orifice to said outlet; provided to the housing; and at least one finger operable member moveable to apply a force directly or indirectly to the drug discharge device for movement along the longitudinal axis towards the discharge block to actuate said discharge mechanism. The housing further defines an aperture through which said at least one finger operable member in part protrudes, and wherein the at least one finger operable member is moveable from a rest position in which the at least one finger operable member acts to block off said aperture to an actuating position in which the aperture is unblocked and through which air may be drawn into the housing in response to patient inhalation through the outlet.

**Related U.S. Application Data**

(60) Provisional application No. 60/823,141, filed on Aug. 22, 2006.

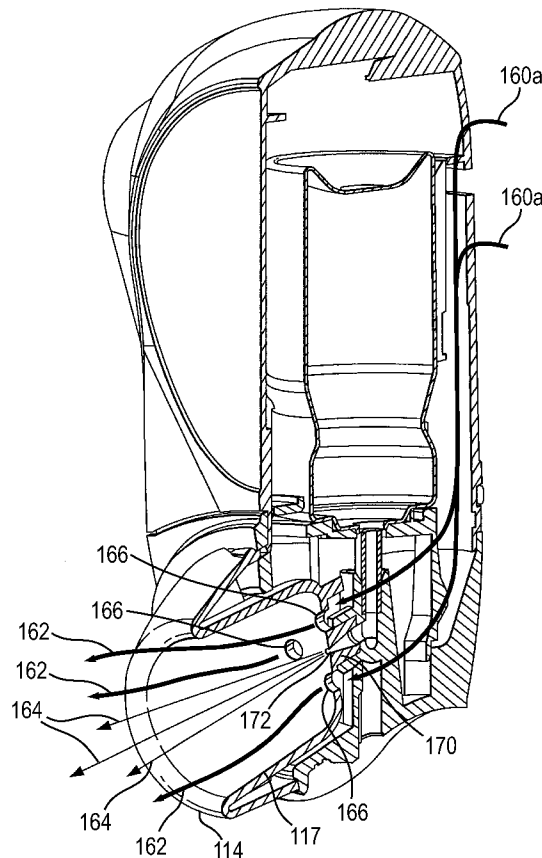
**Publication Classification**(51) **Int. Cl.**  
**A61M 11/00** (2006.01)  
**A61M 15/00** (2006.01)

FIG. 1

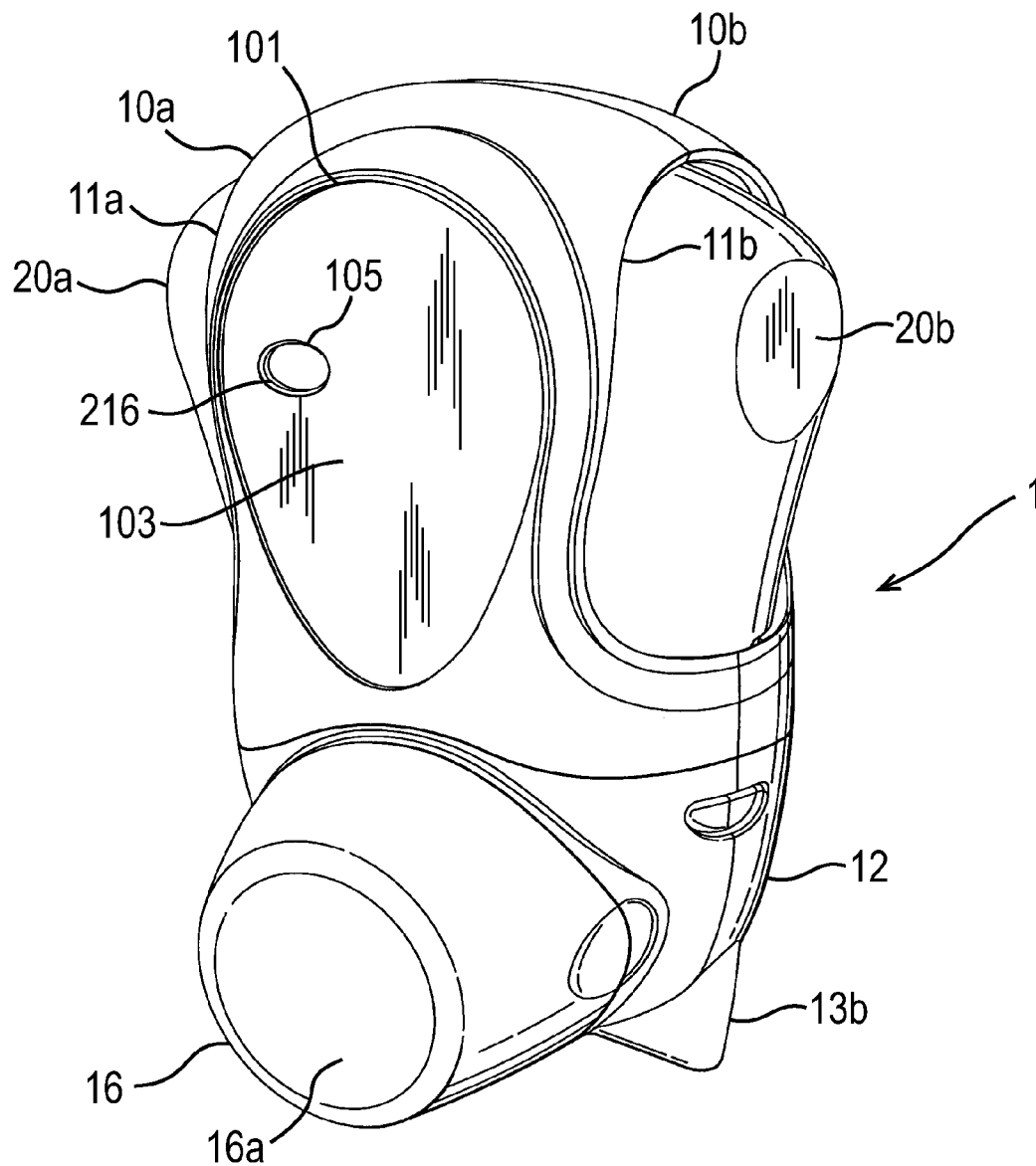


FIG. 2

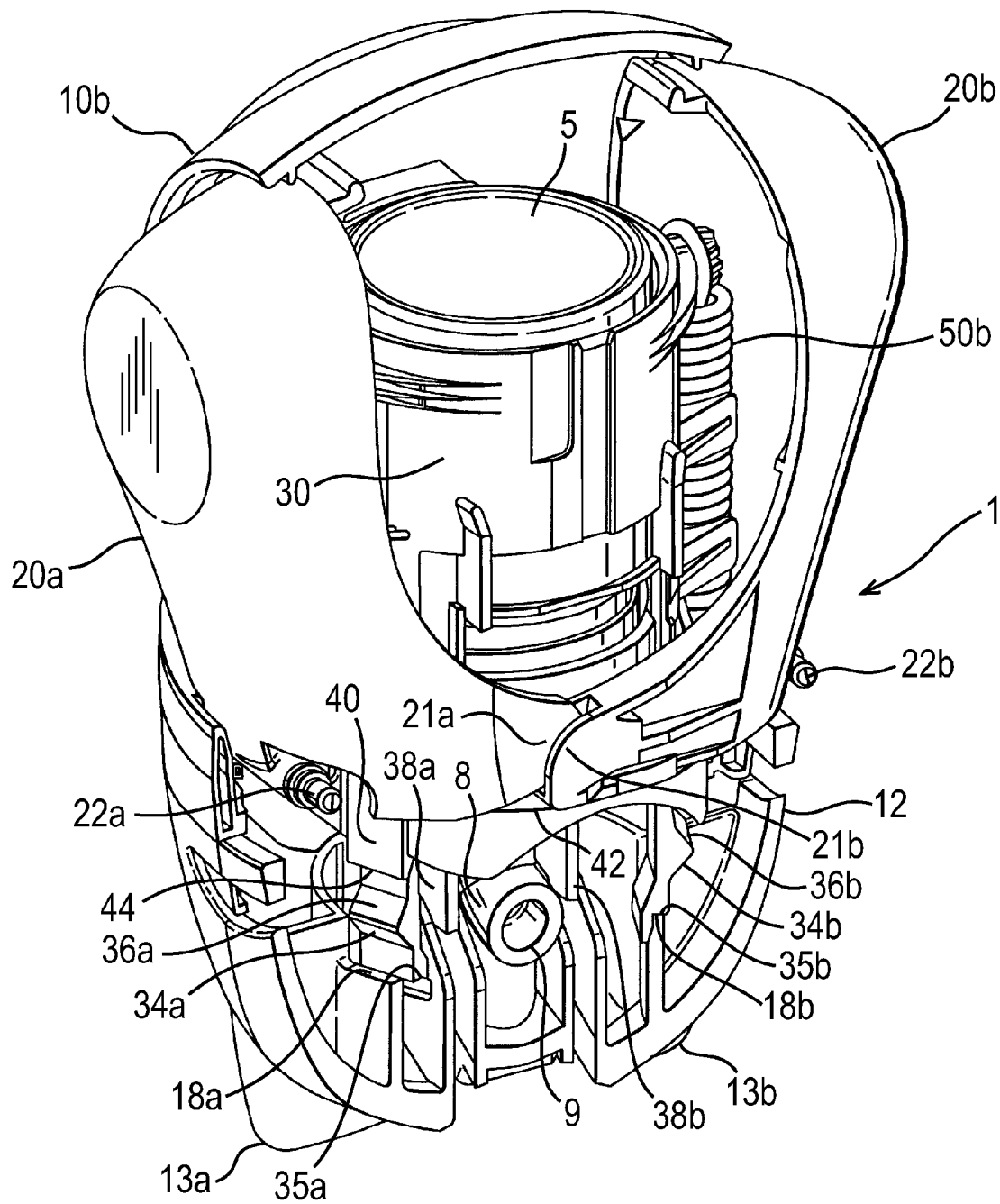


FIG. 3a

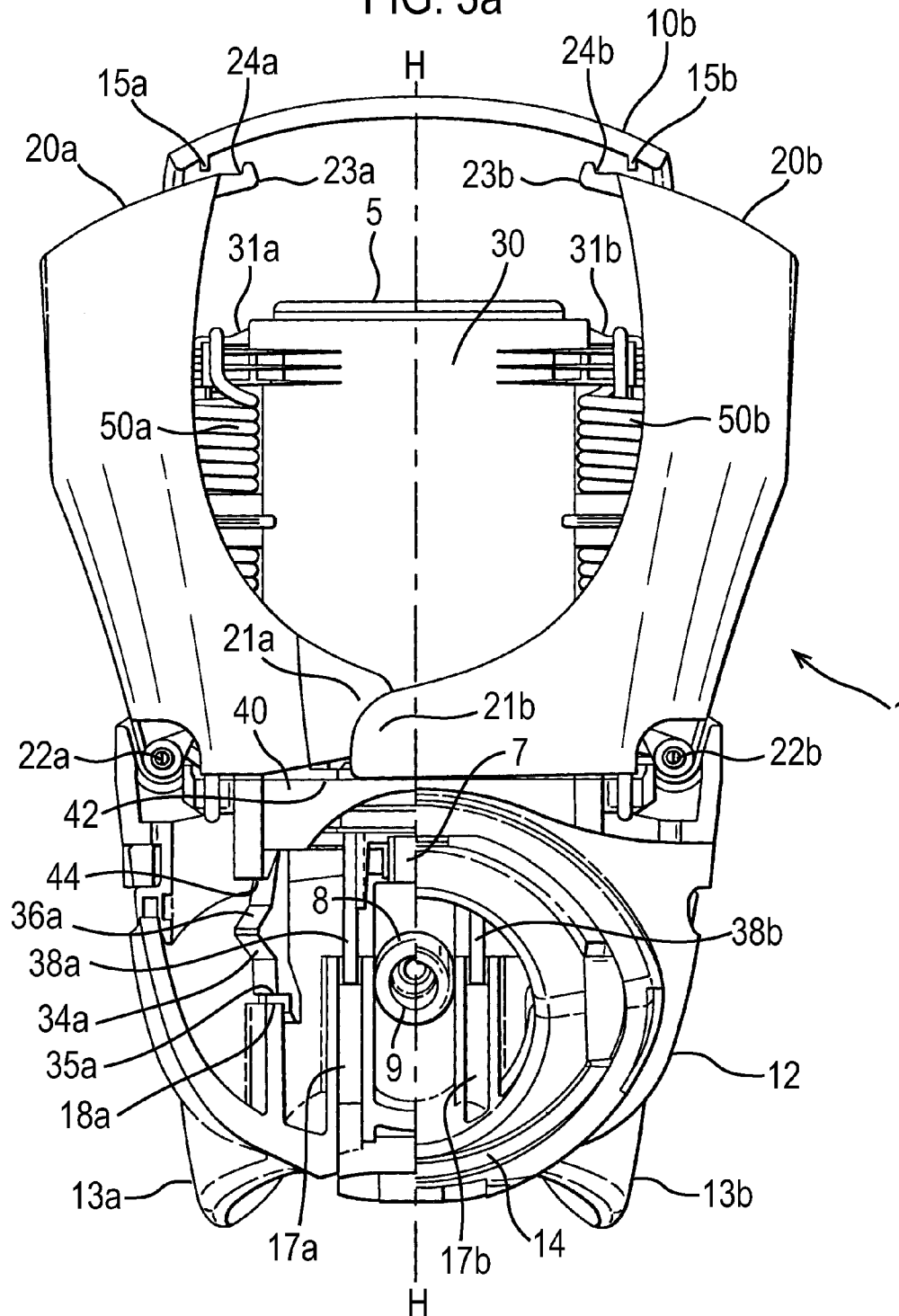


FIG. 3b

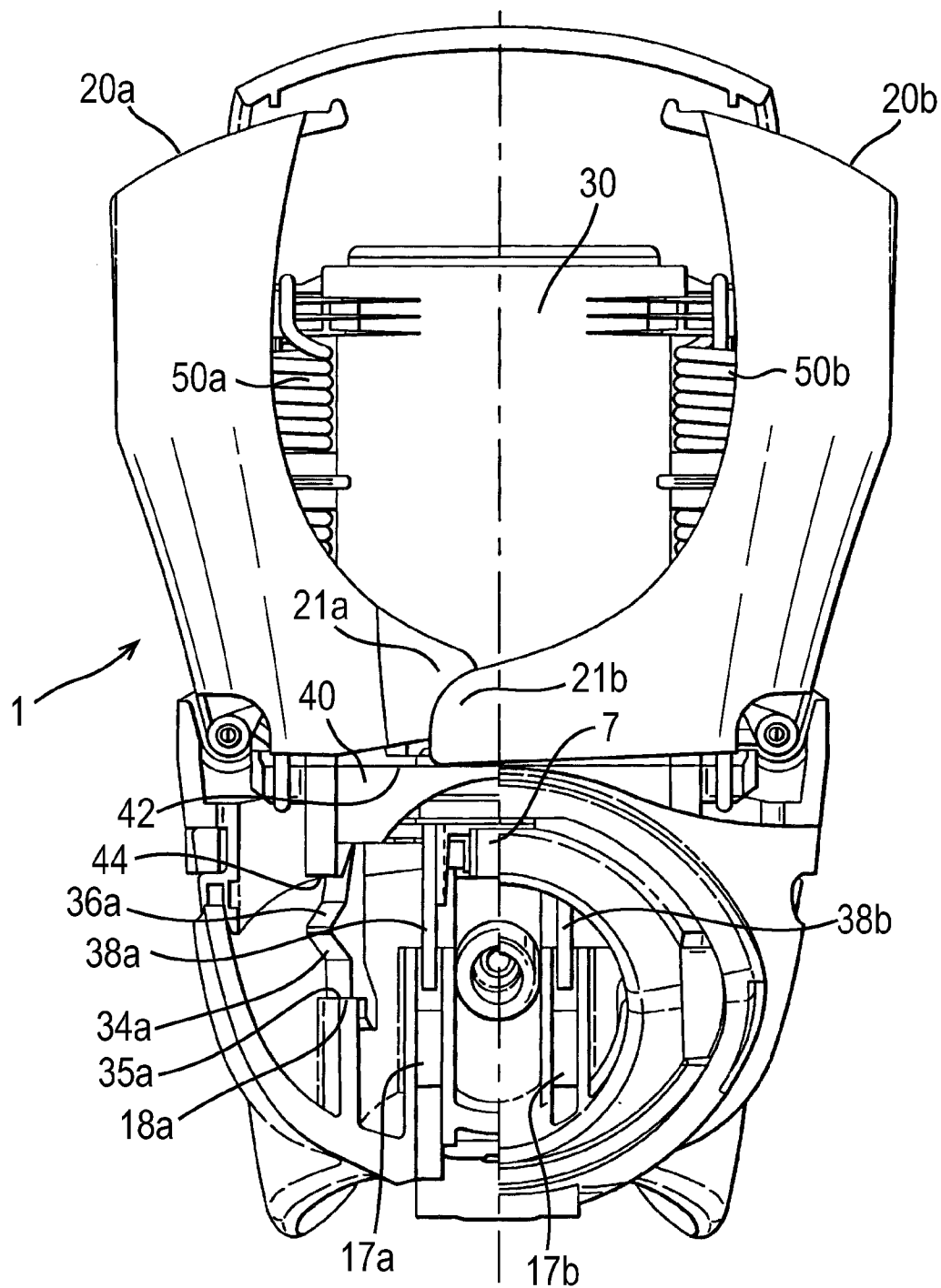


FIG. 4a

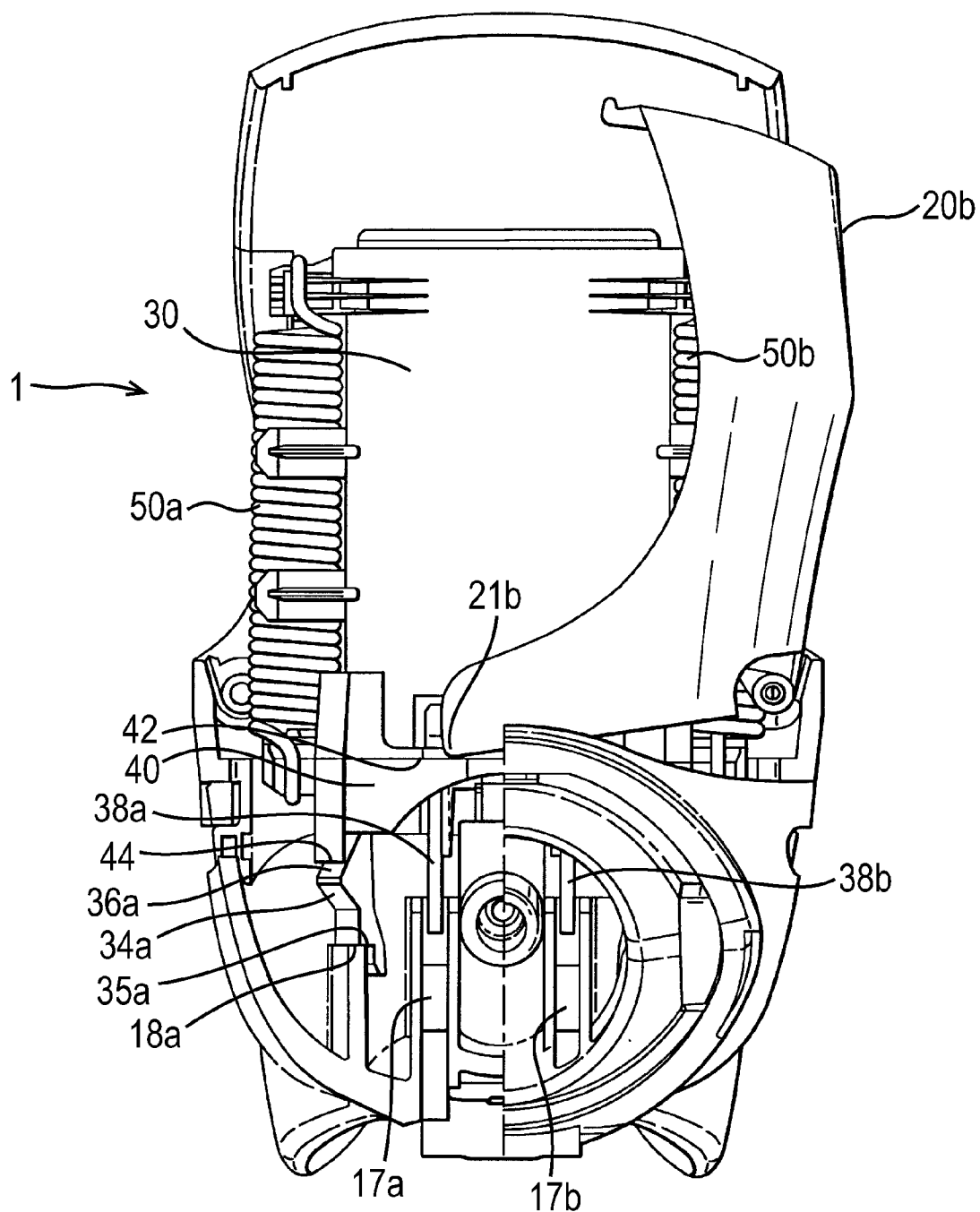


FIG. 4b

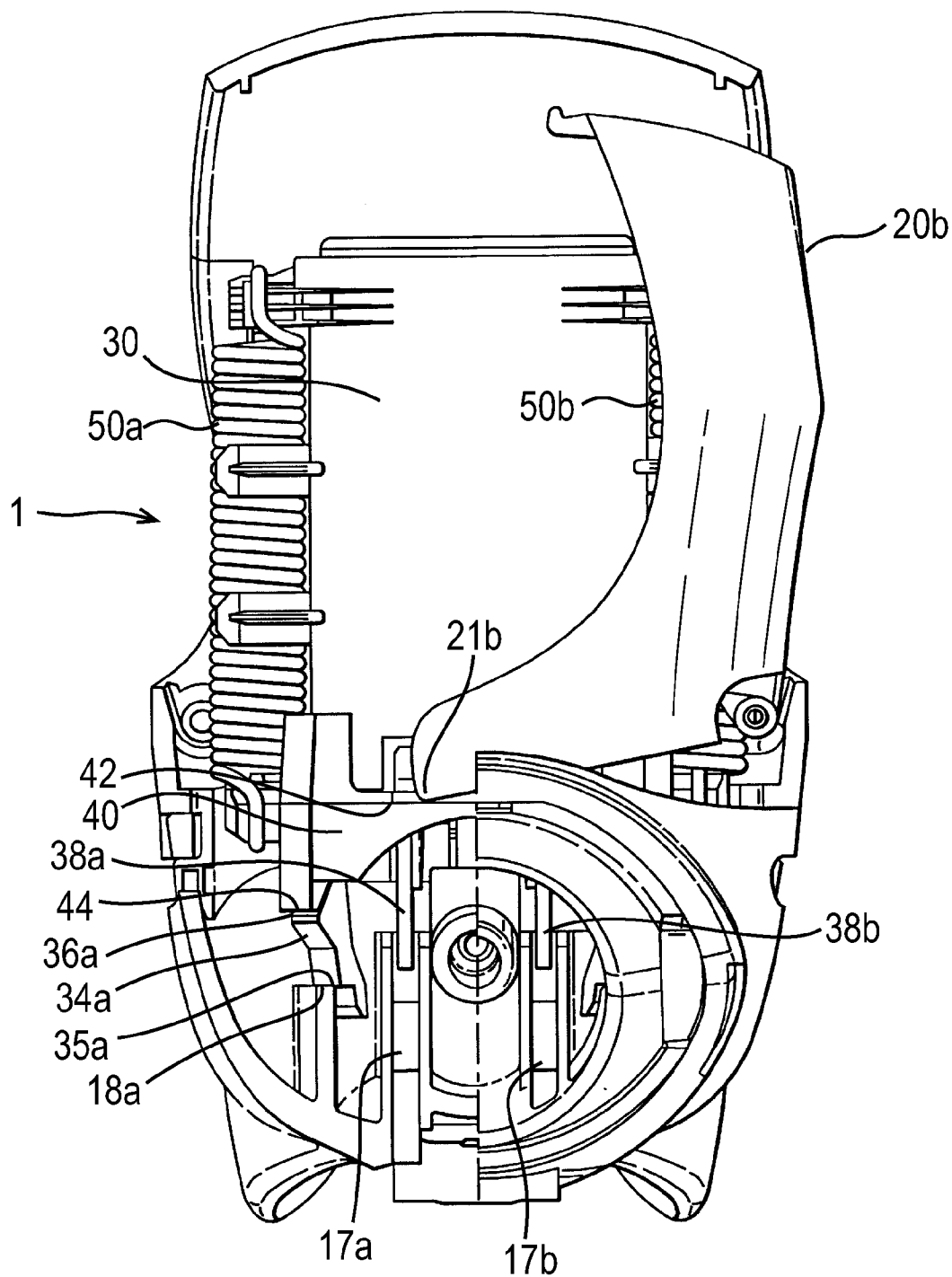




FIG. 4c

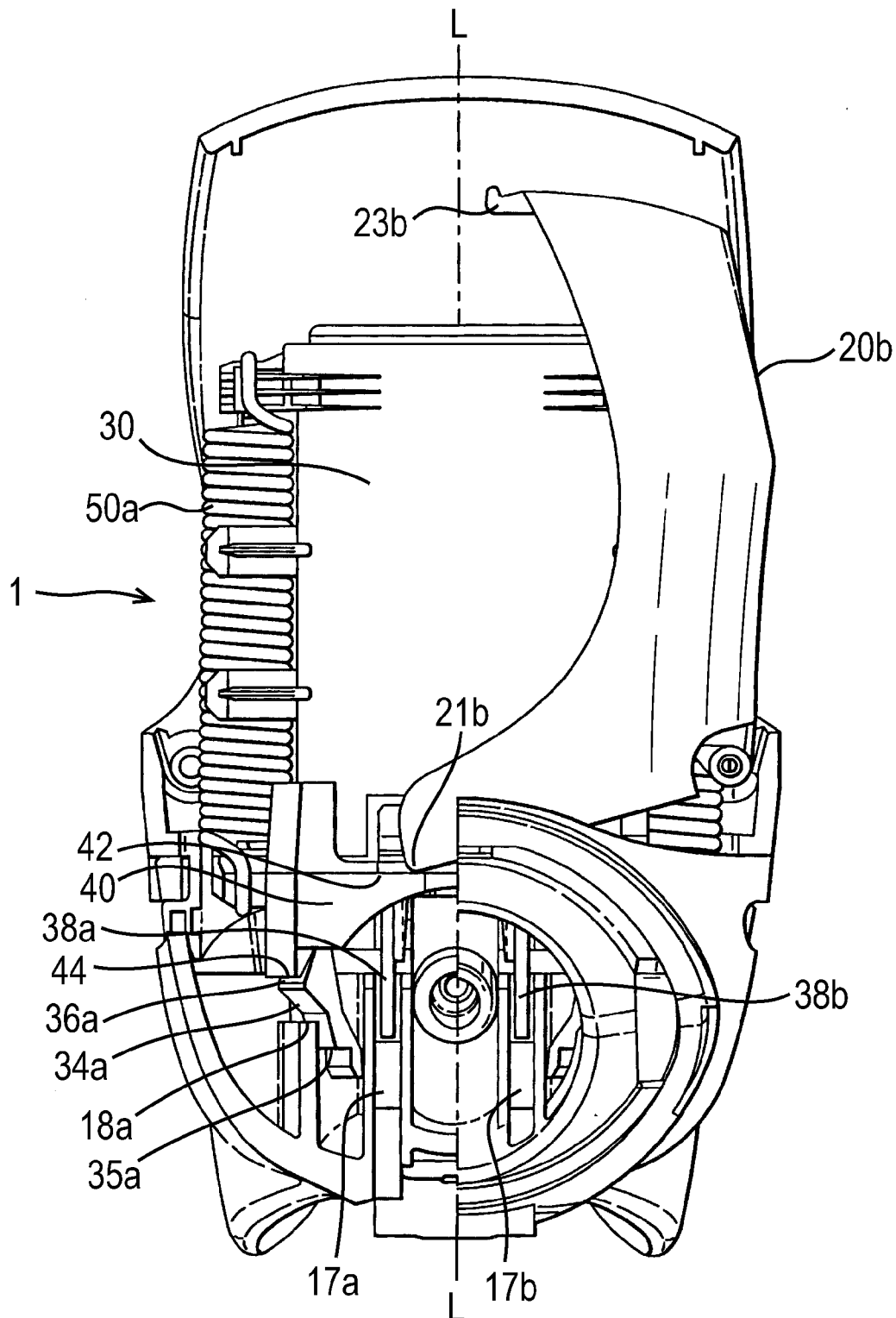


FIG. 5

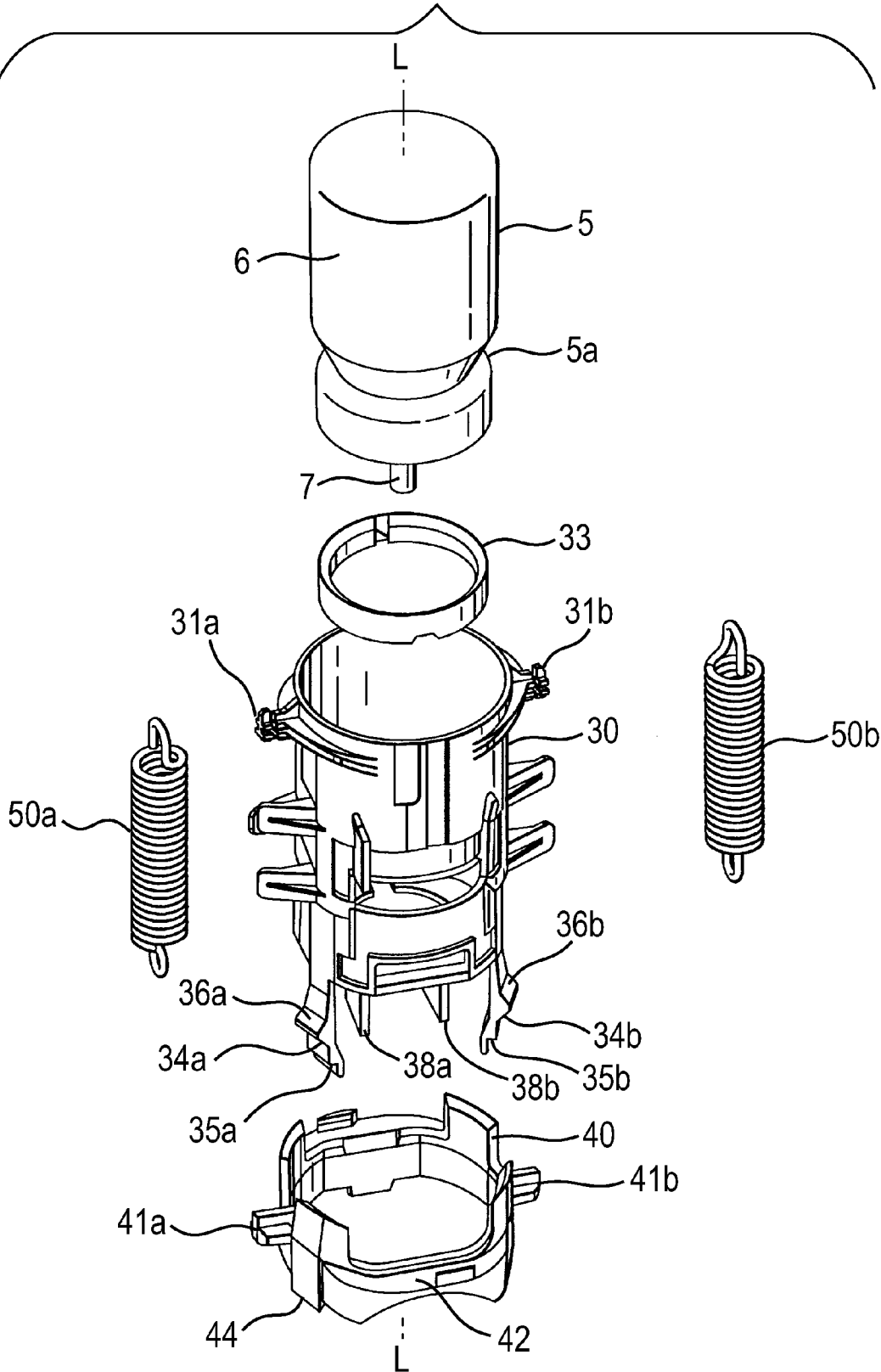


FIG. 6

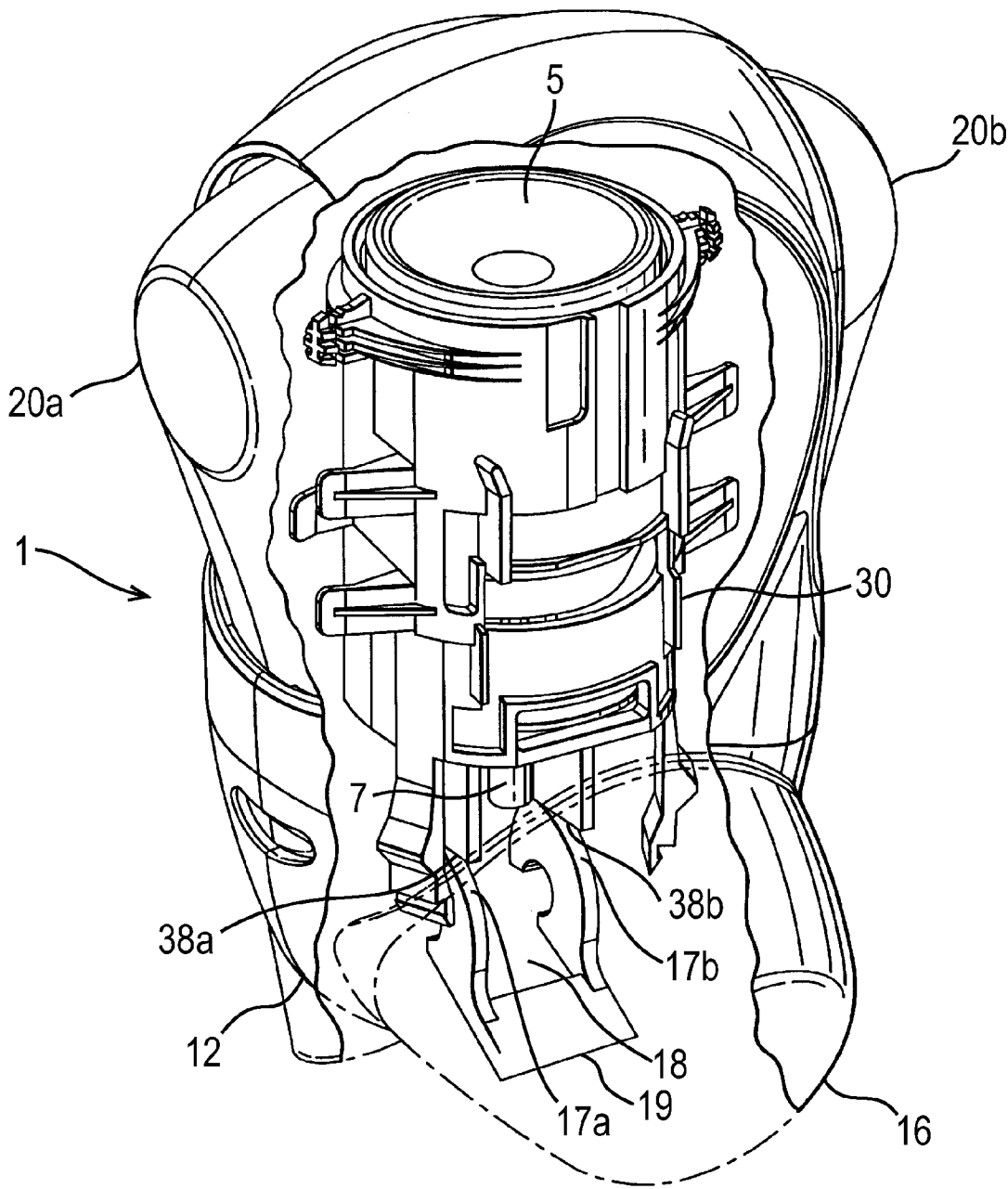


FIG. 7

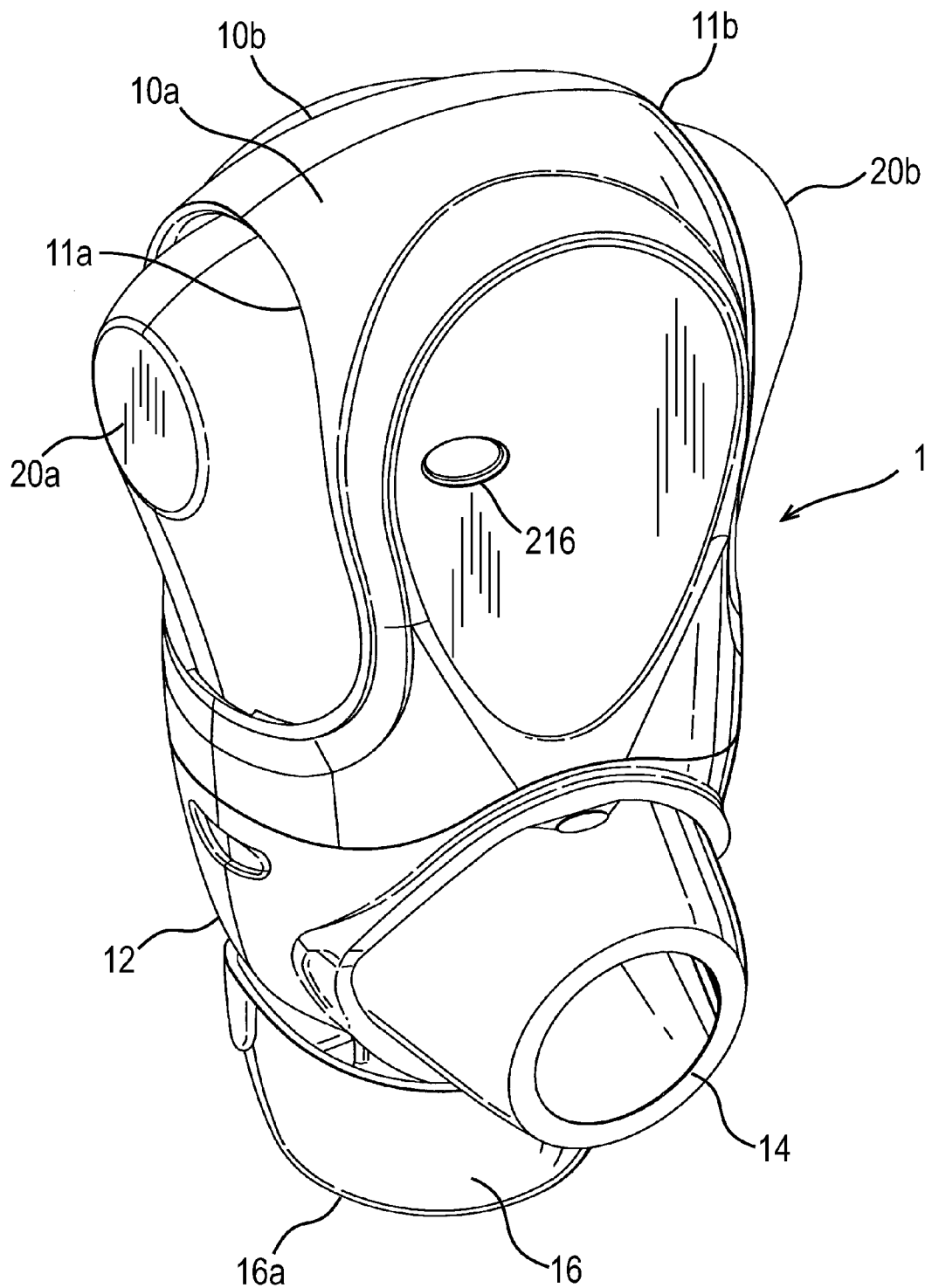


FIG. 8

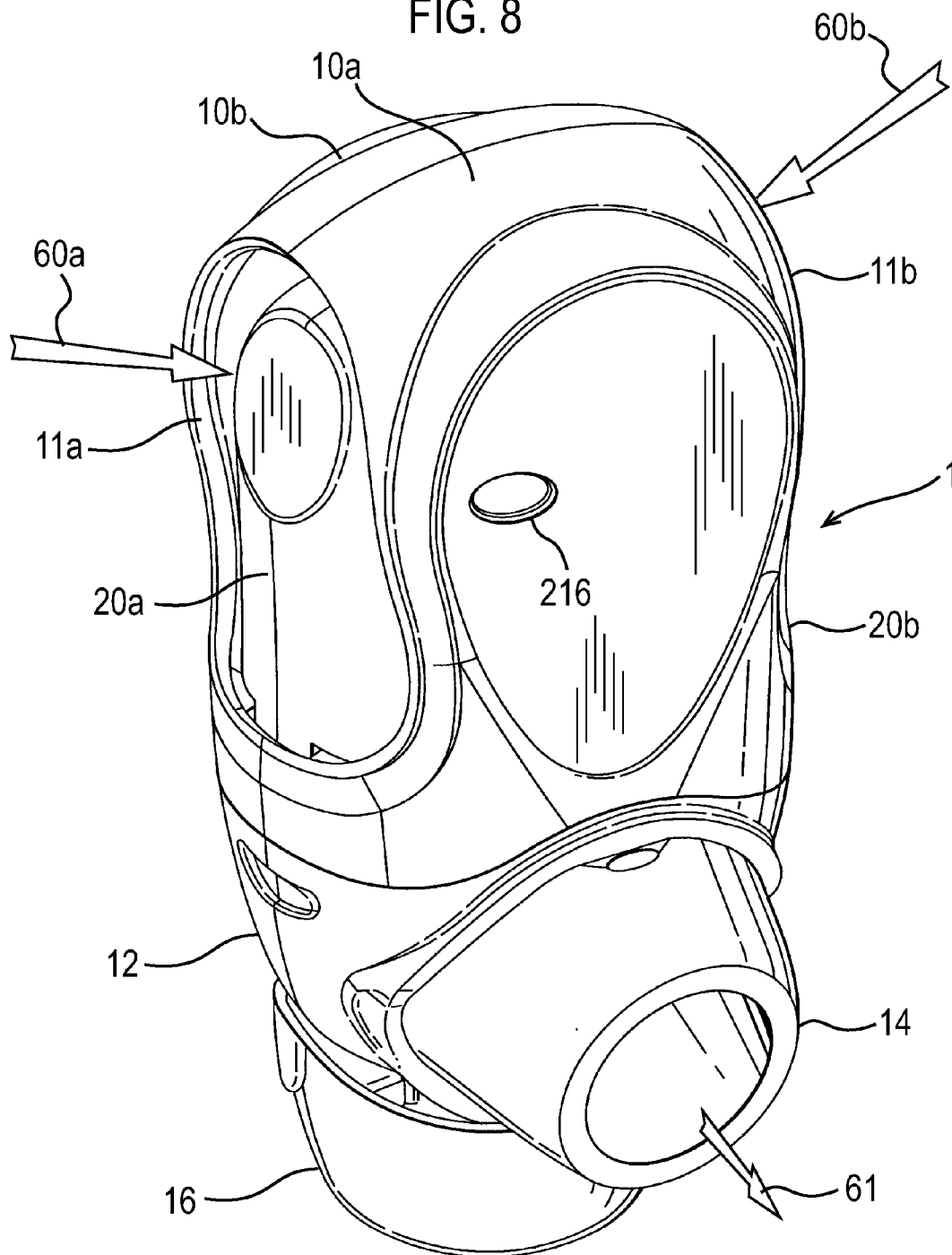


FIG. 9

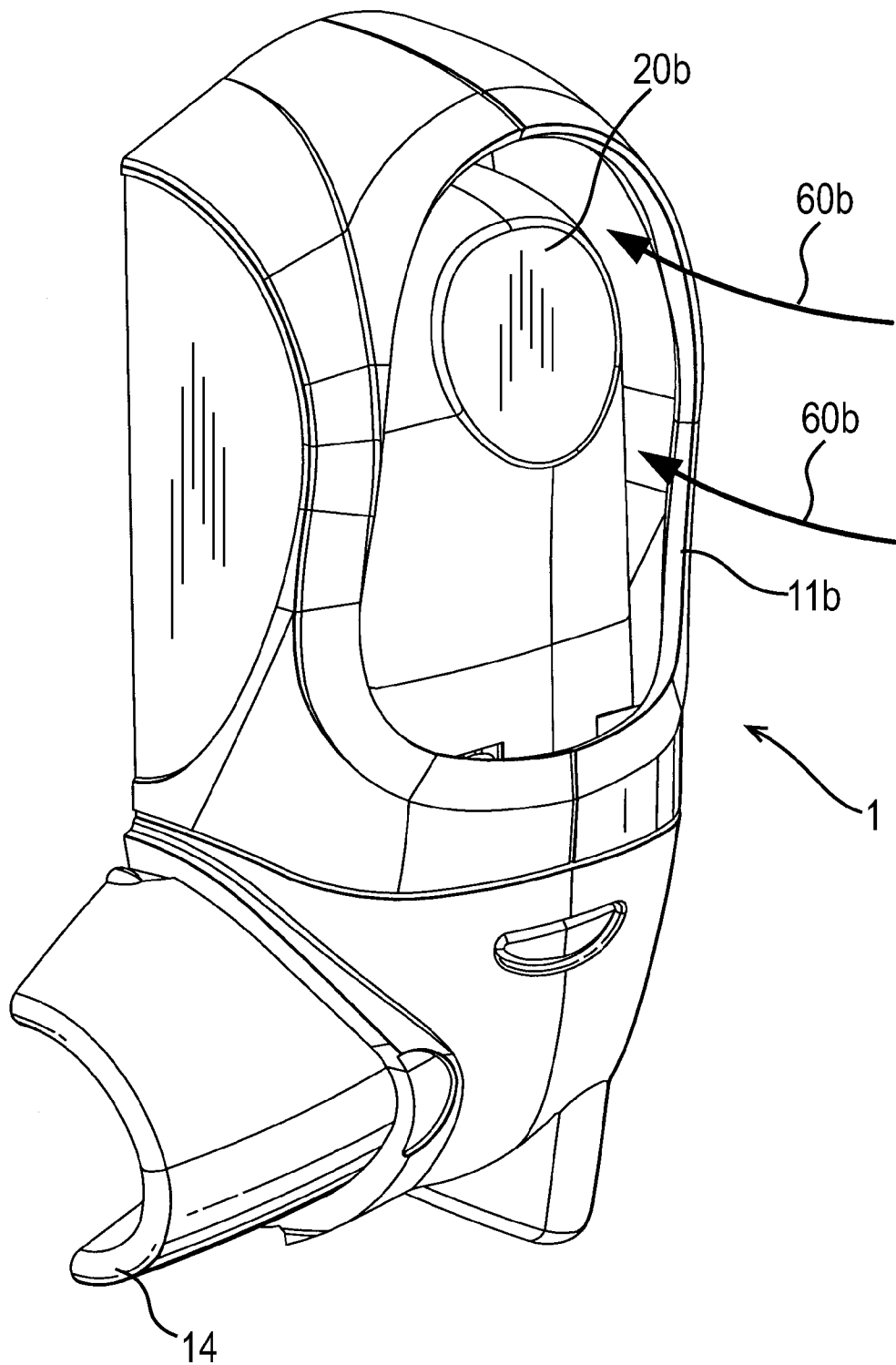


FIG. 10

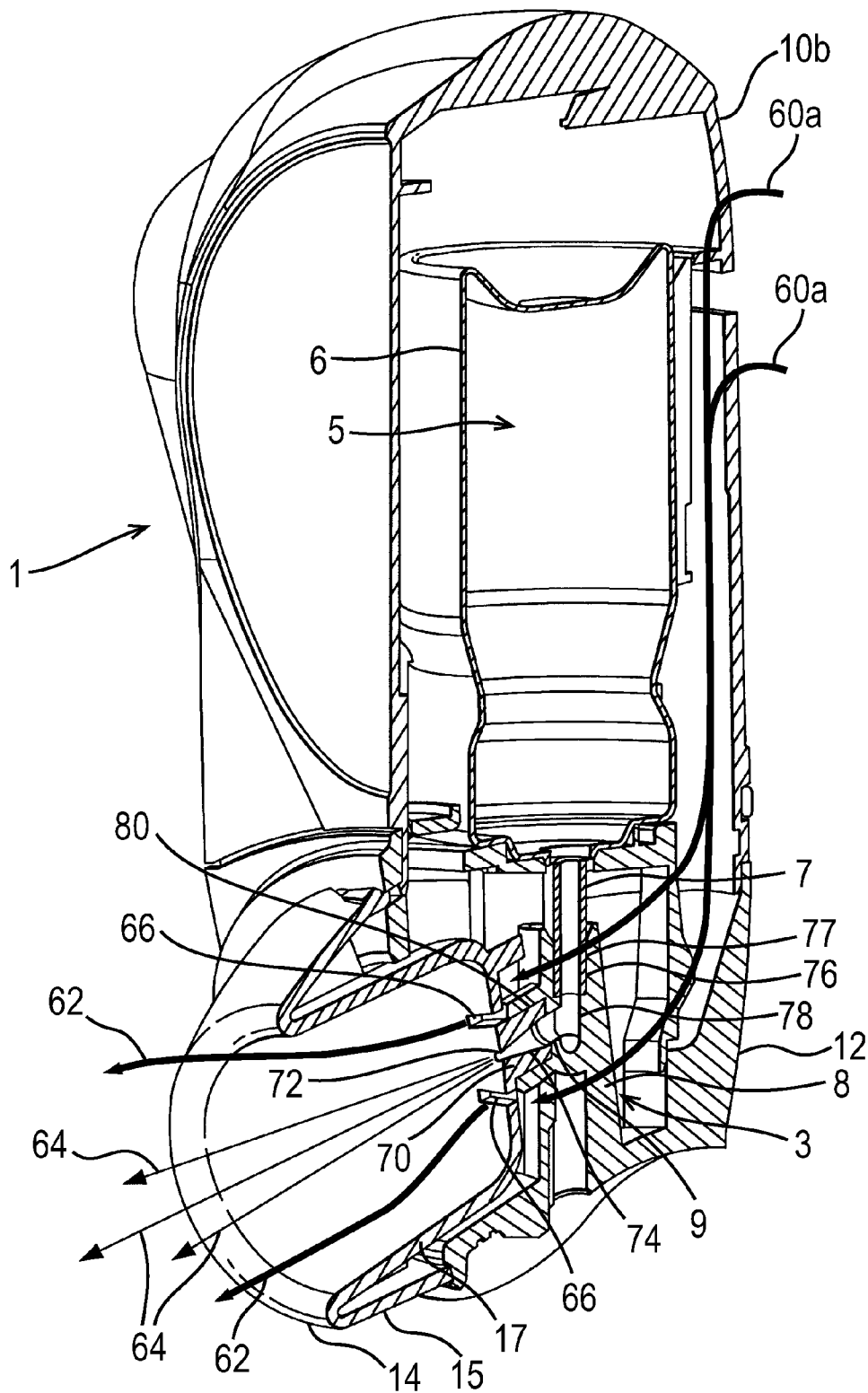


FIG. 11

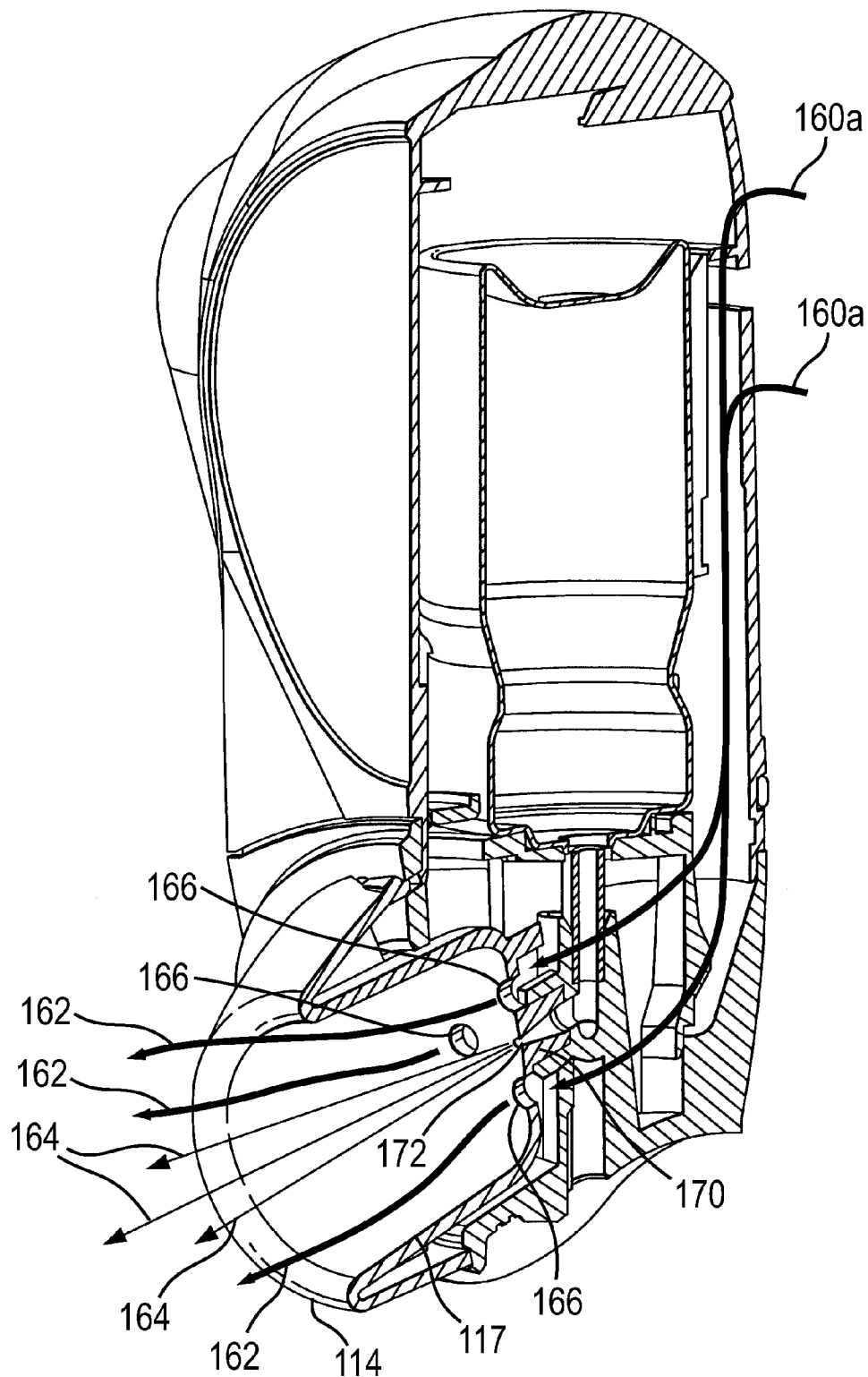
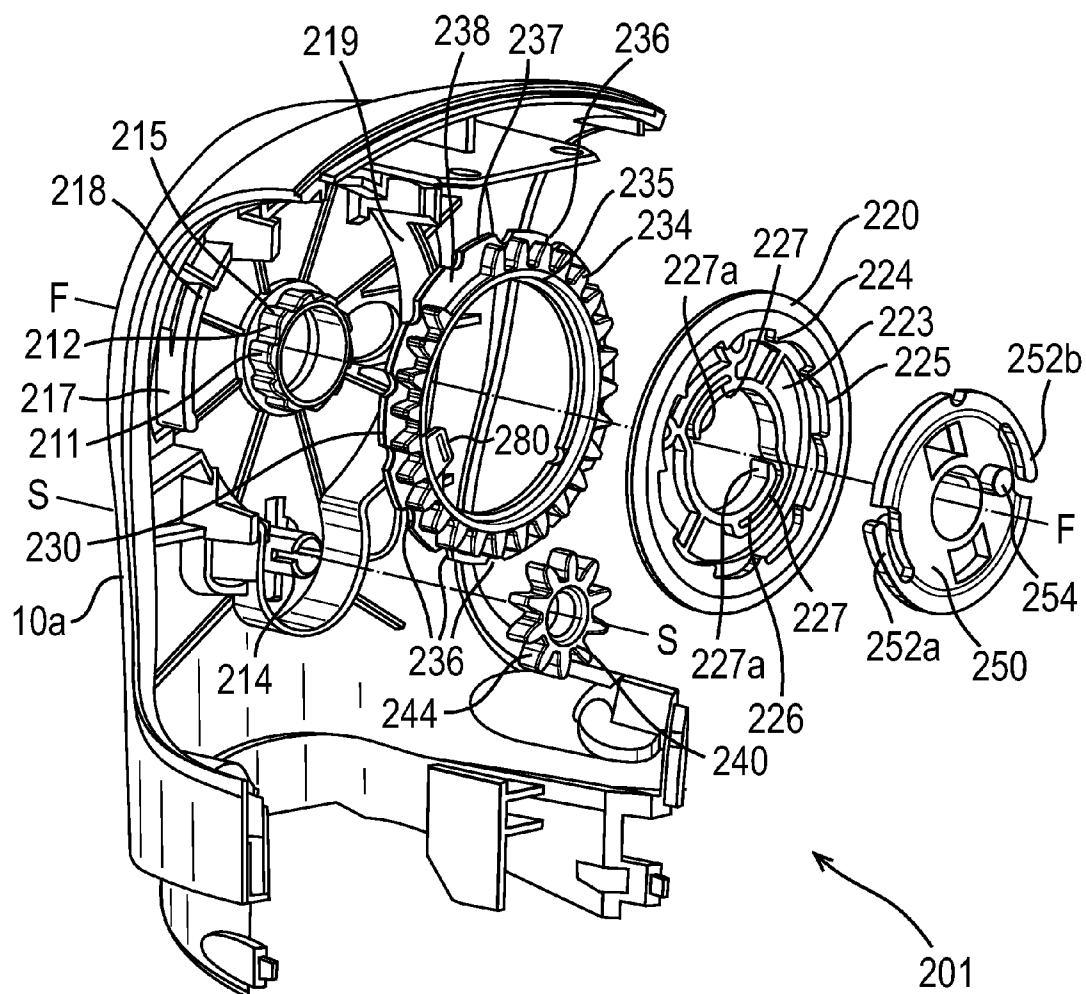




FIG. 12



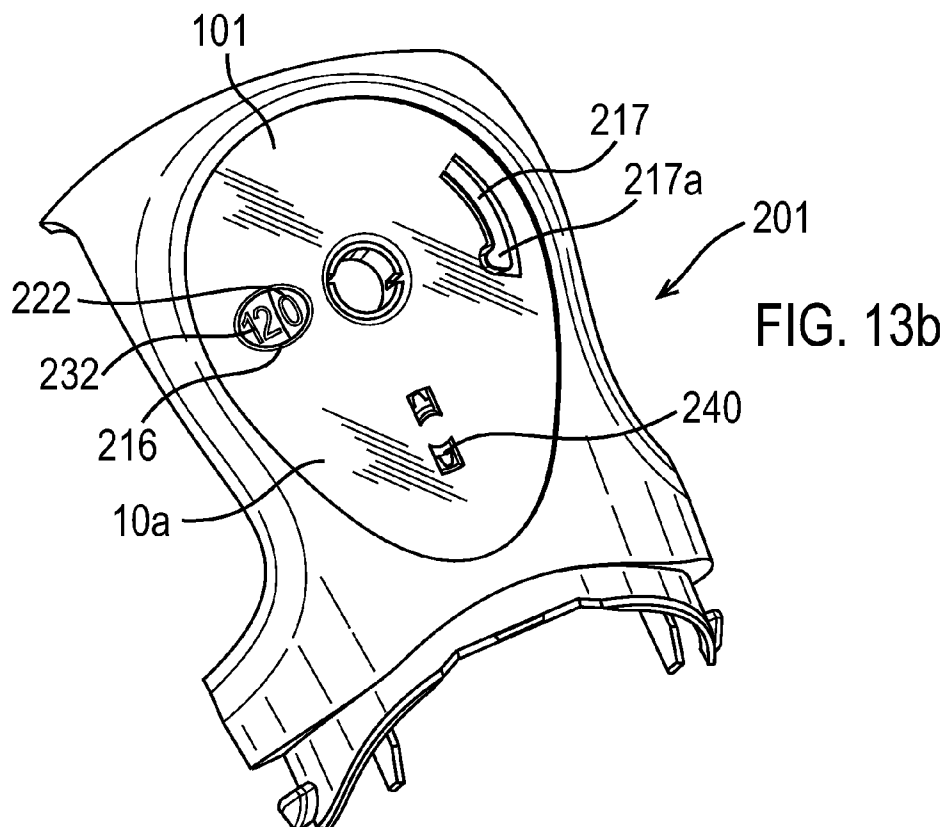
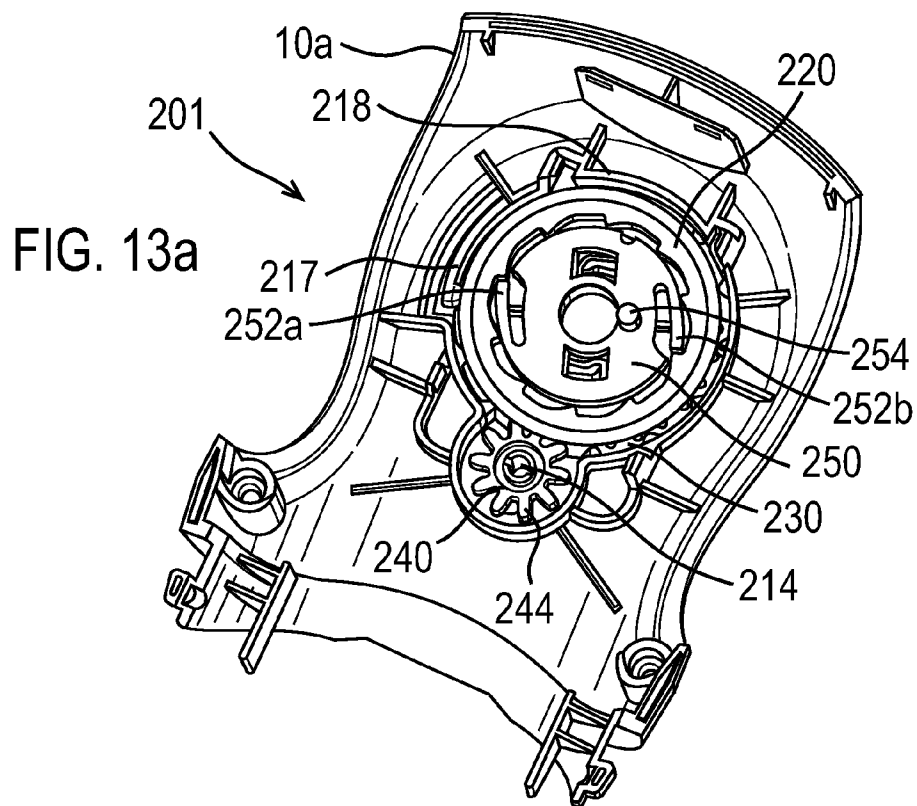


FIG. 14a

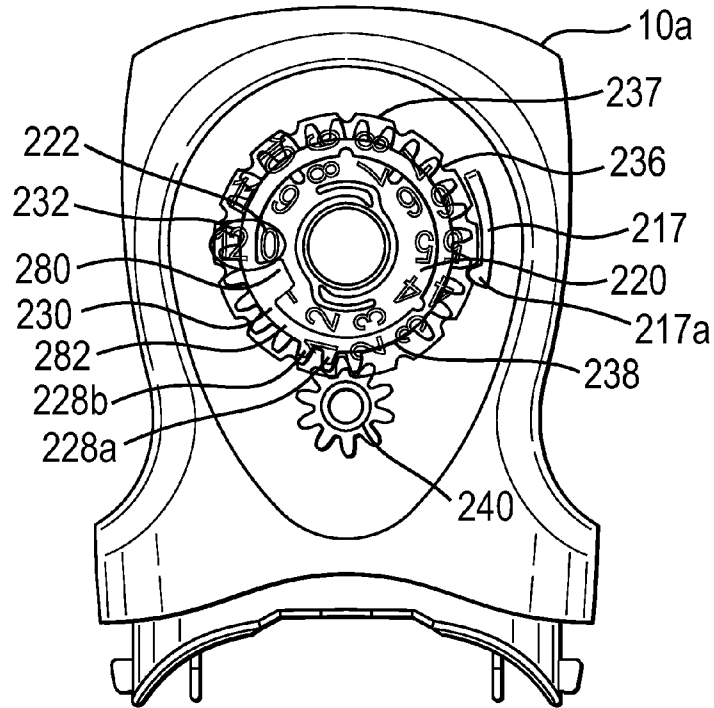


FIG. 14b

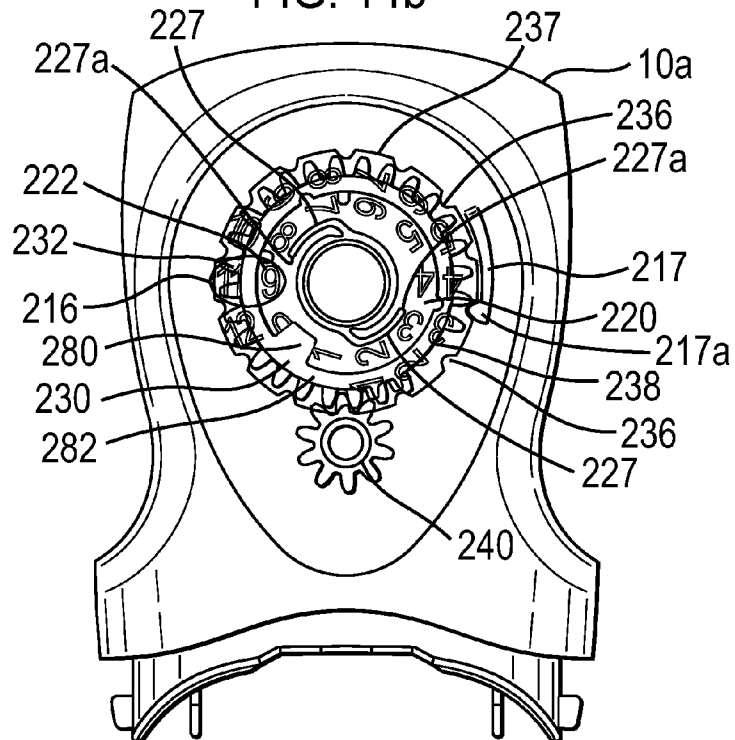


FIG. 15a

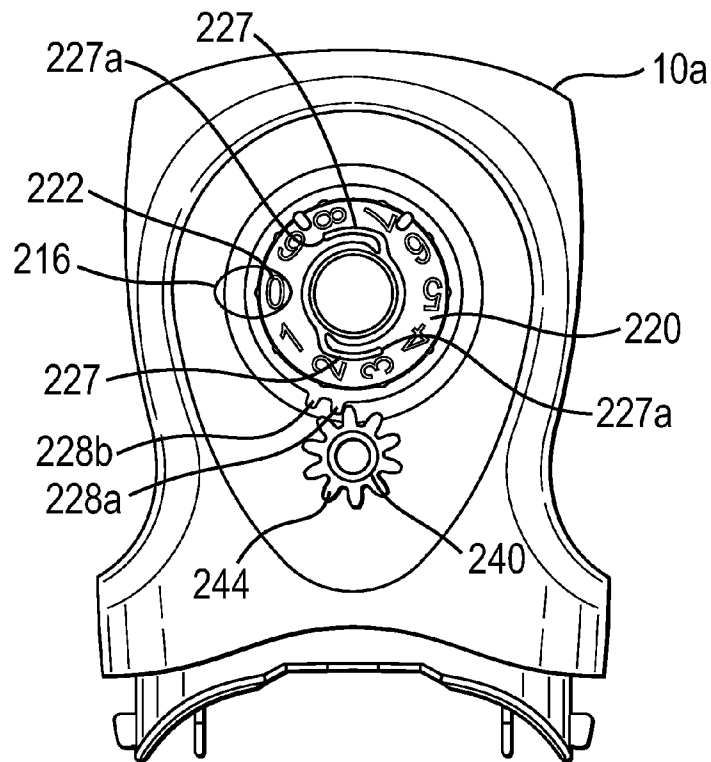


FIG. 15b

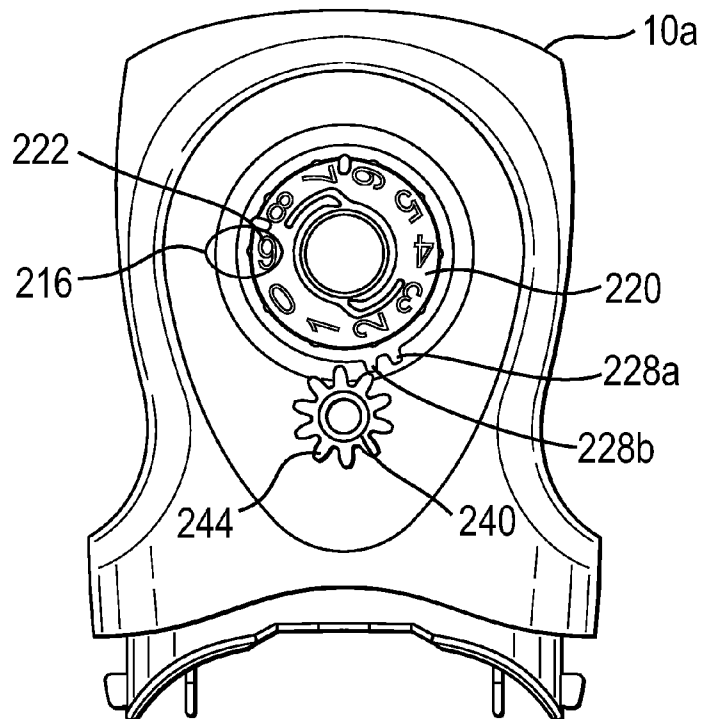


FIG. 16a

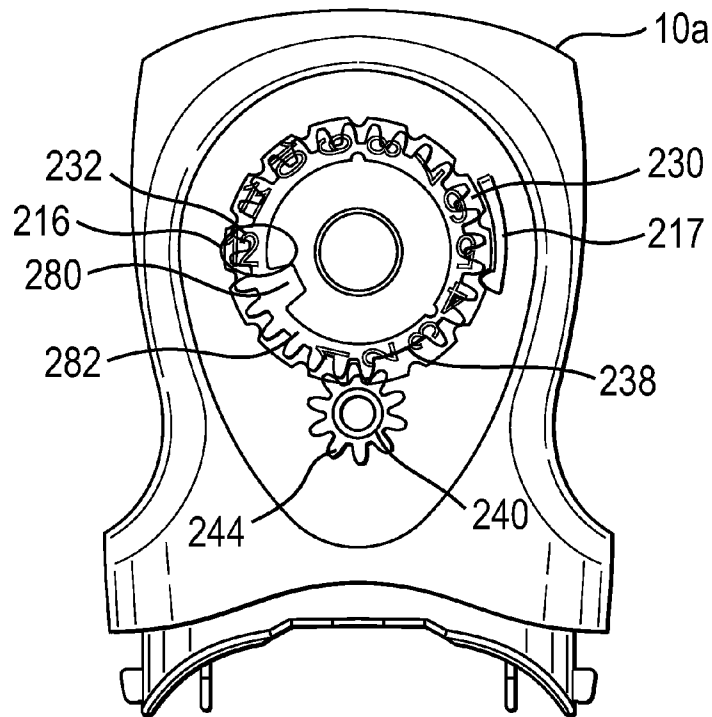


FIG. 16b

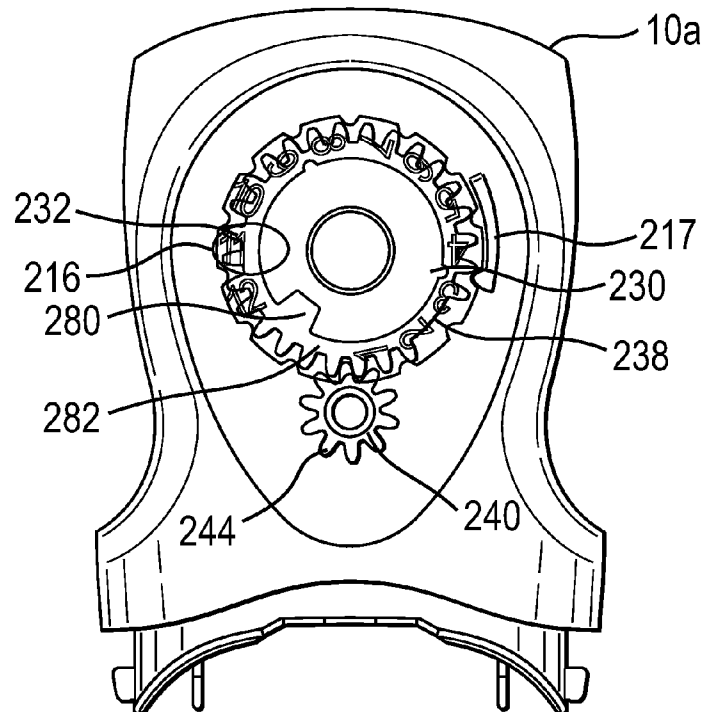


FIG. 17a

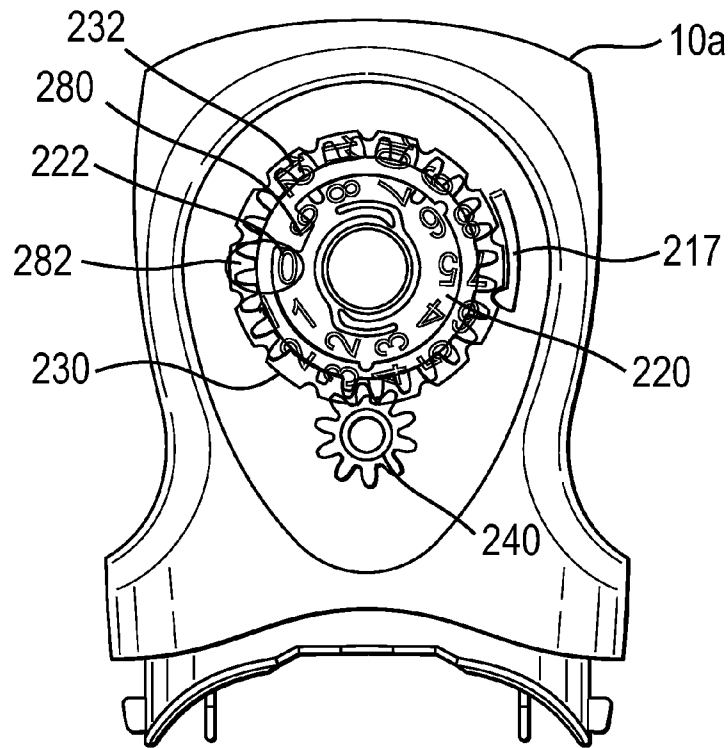


FIG. 17b

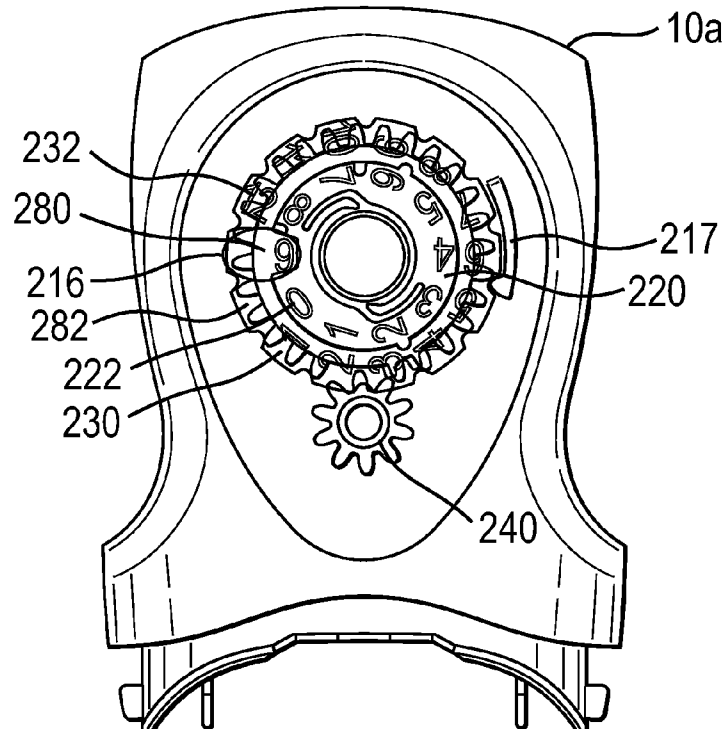


FIG. 18a

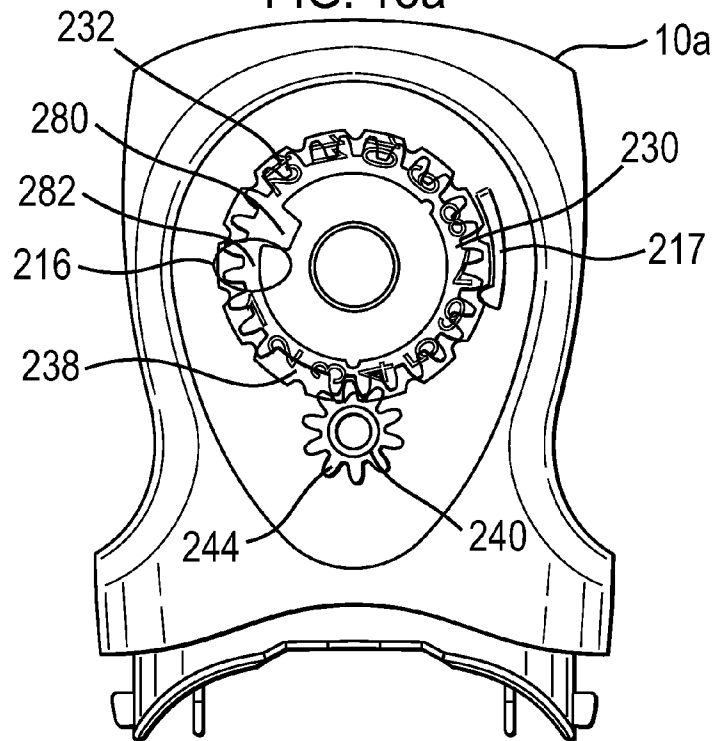


FIG. 18b

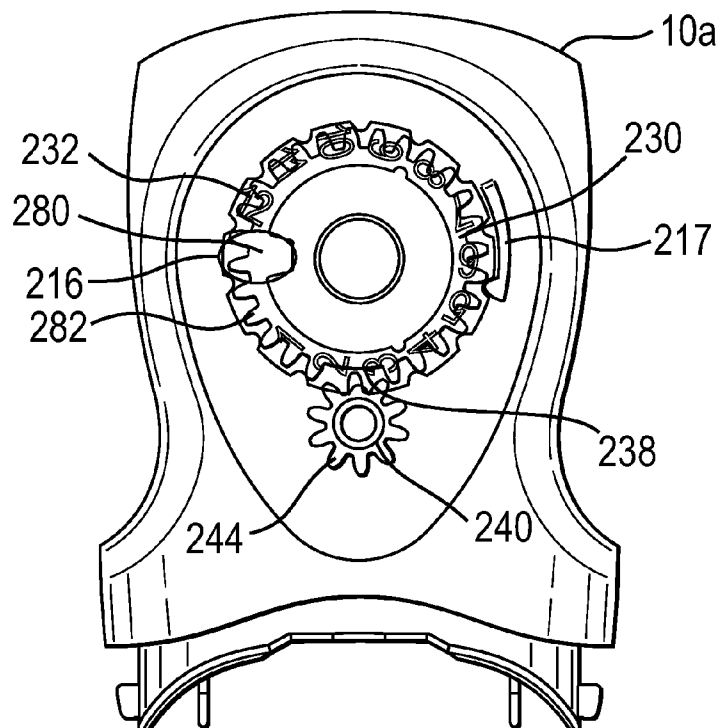


FIG. 19

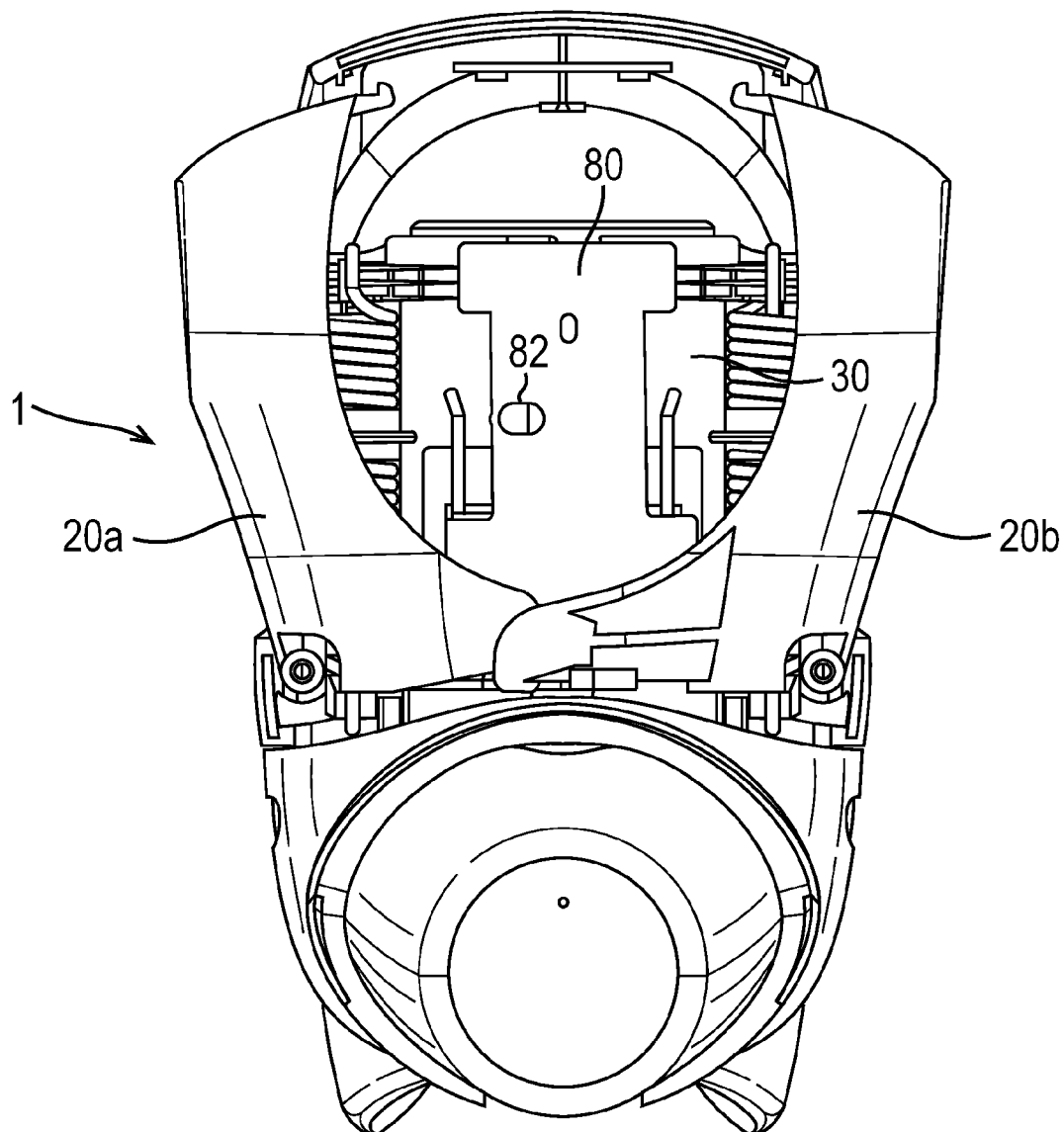




FIG. 20

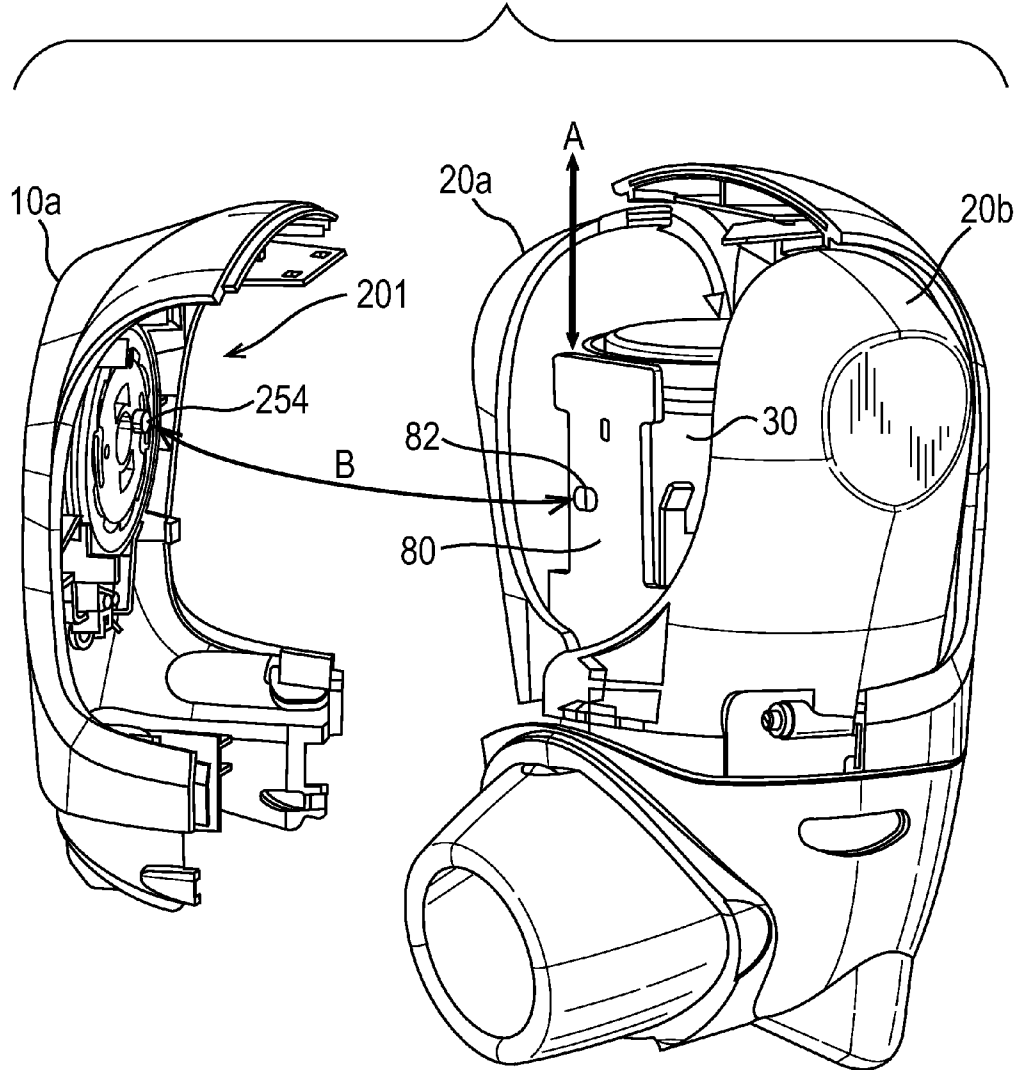
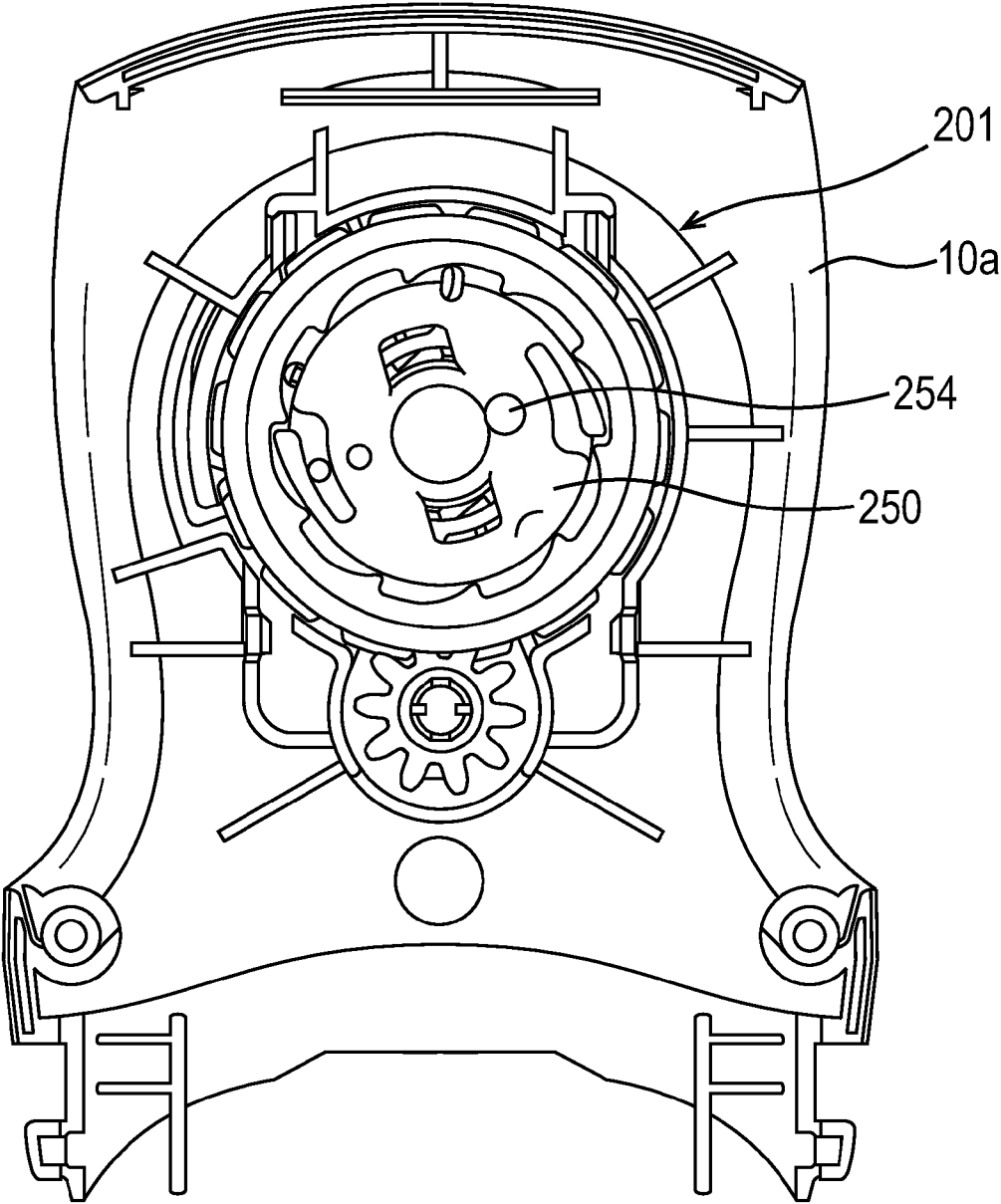
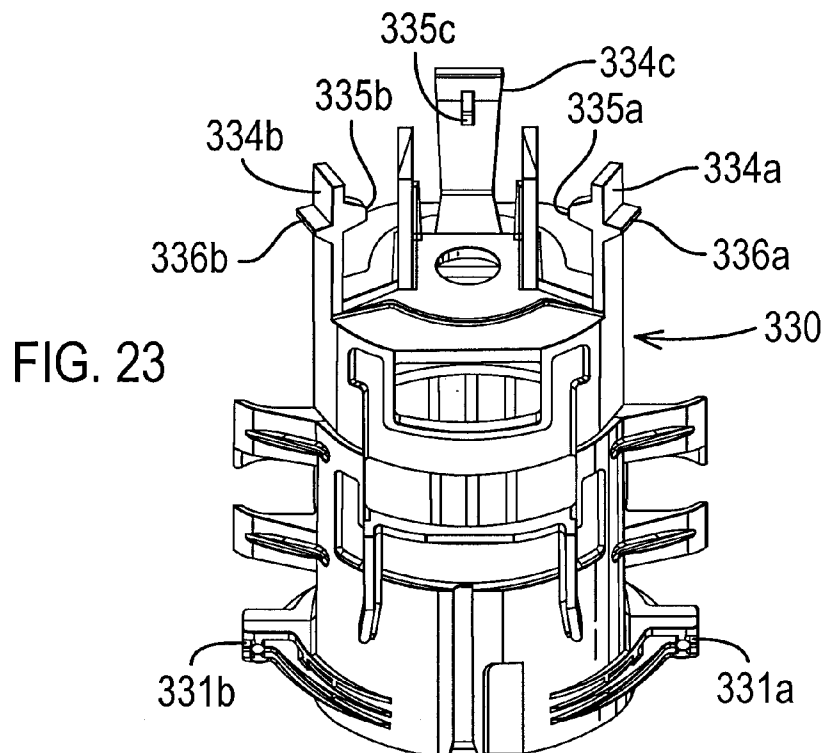
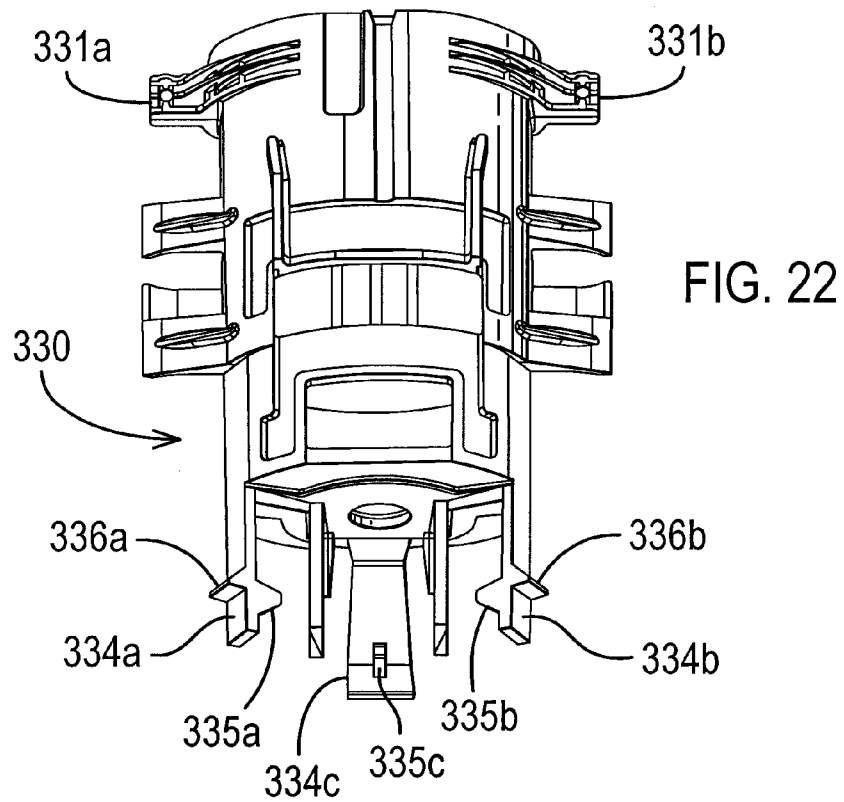
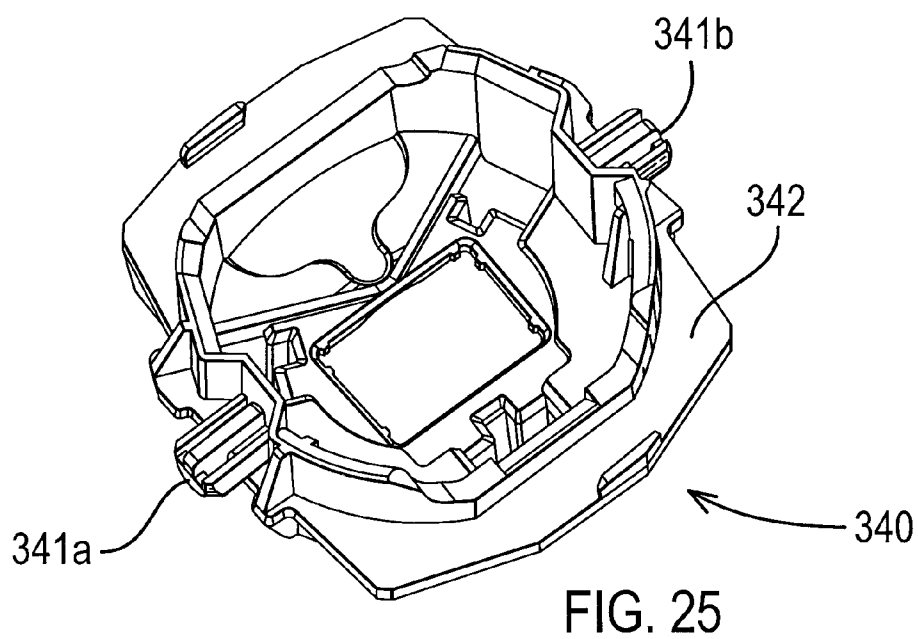
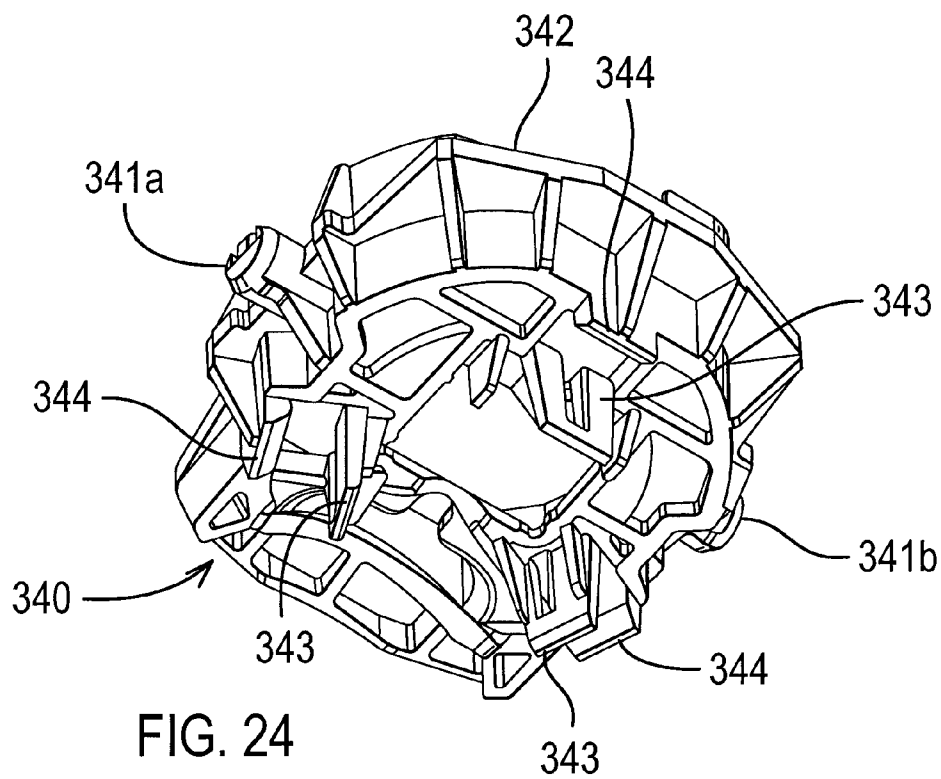
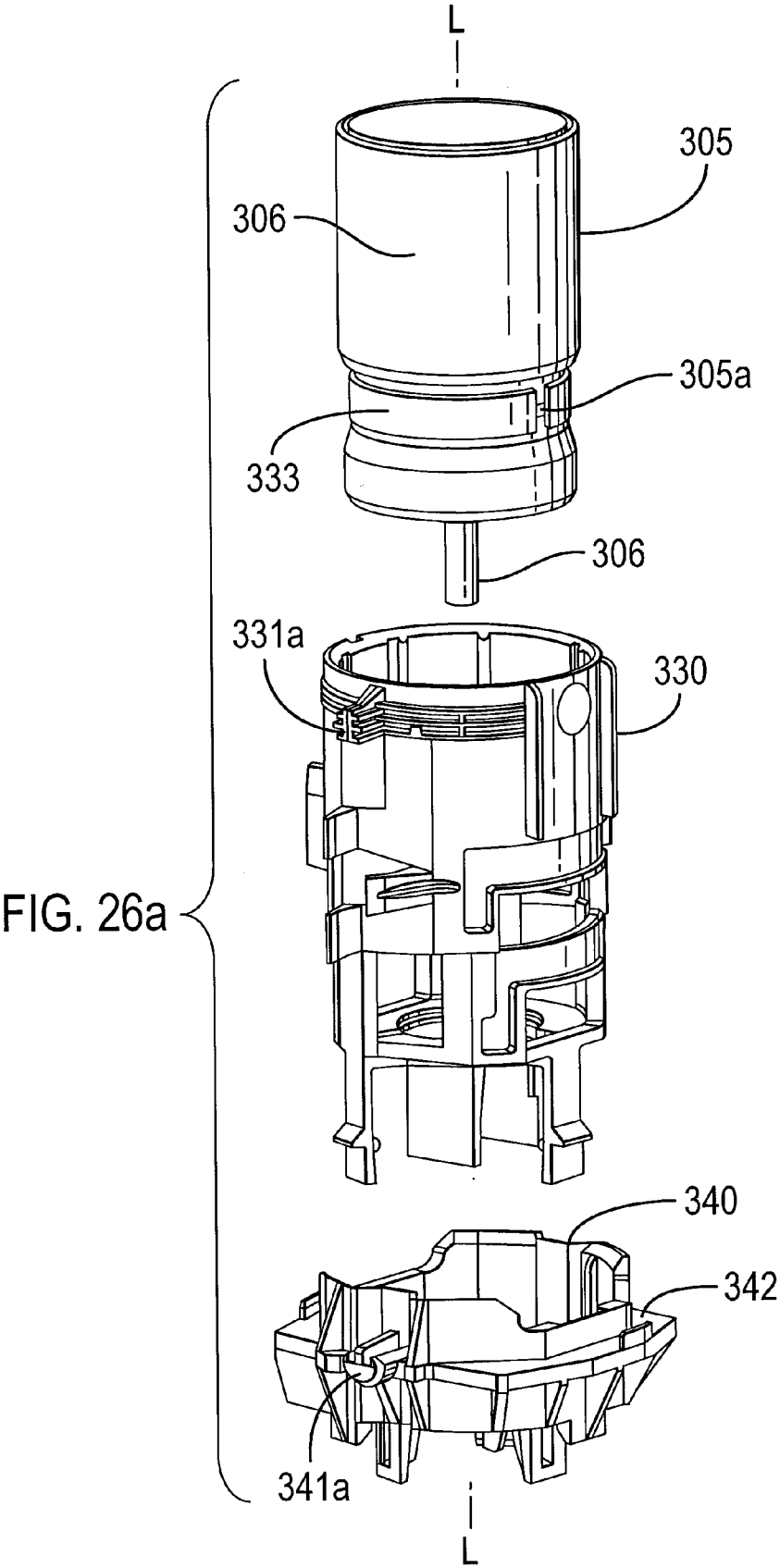


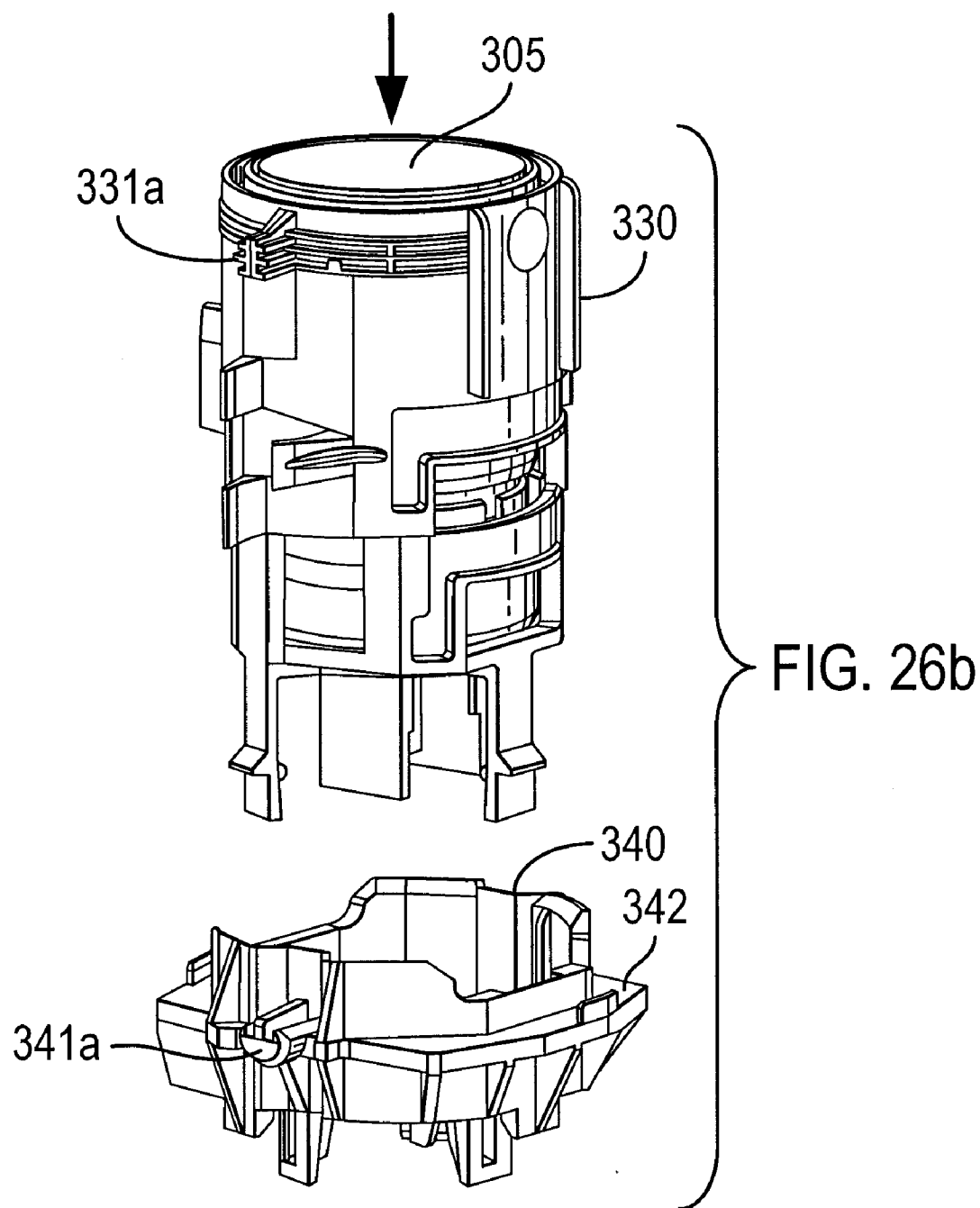
FIG. 21











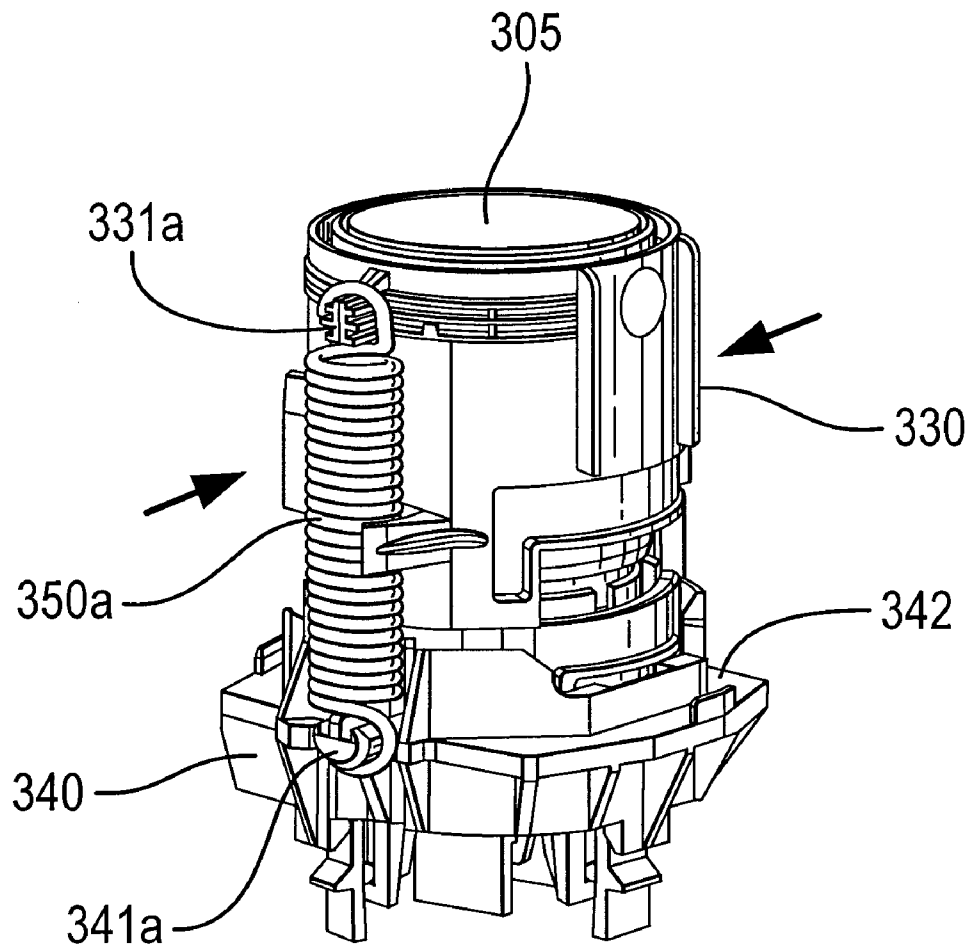


FIG. 26c

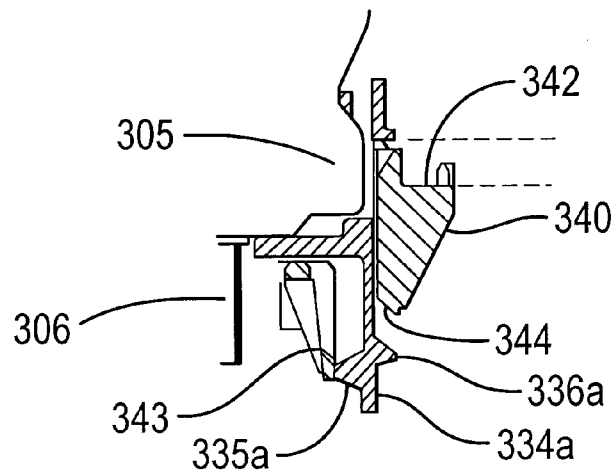


FIG. 27a

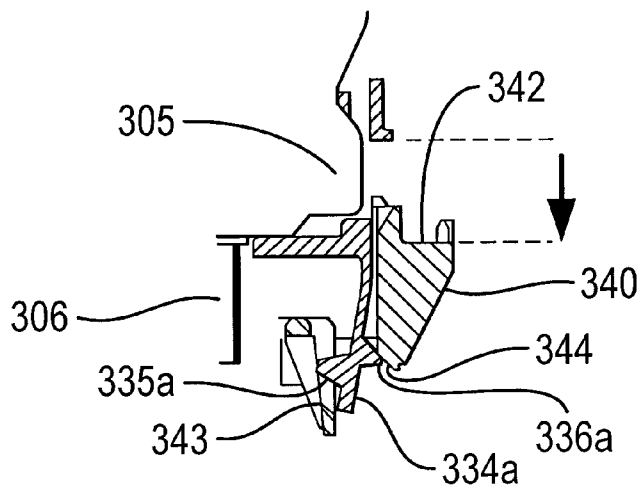


FIG. 27b

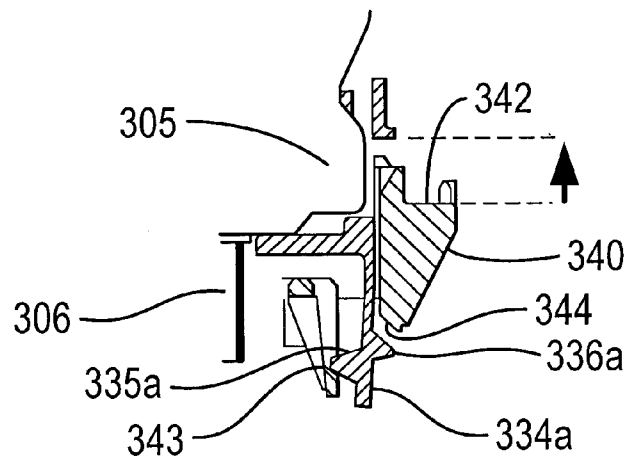


FIG. 27c



FIG. 28

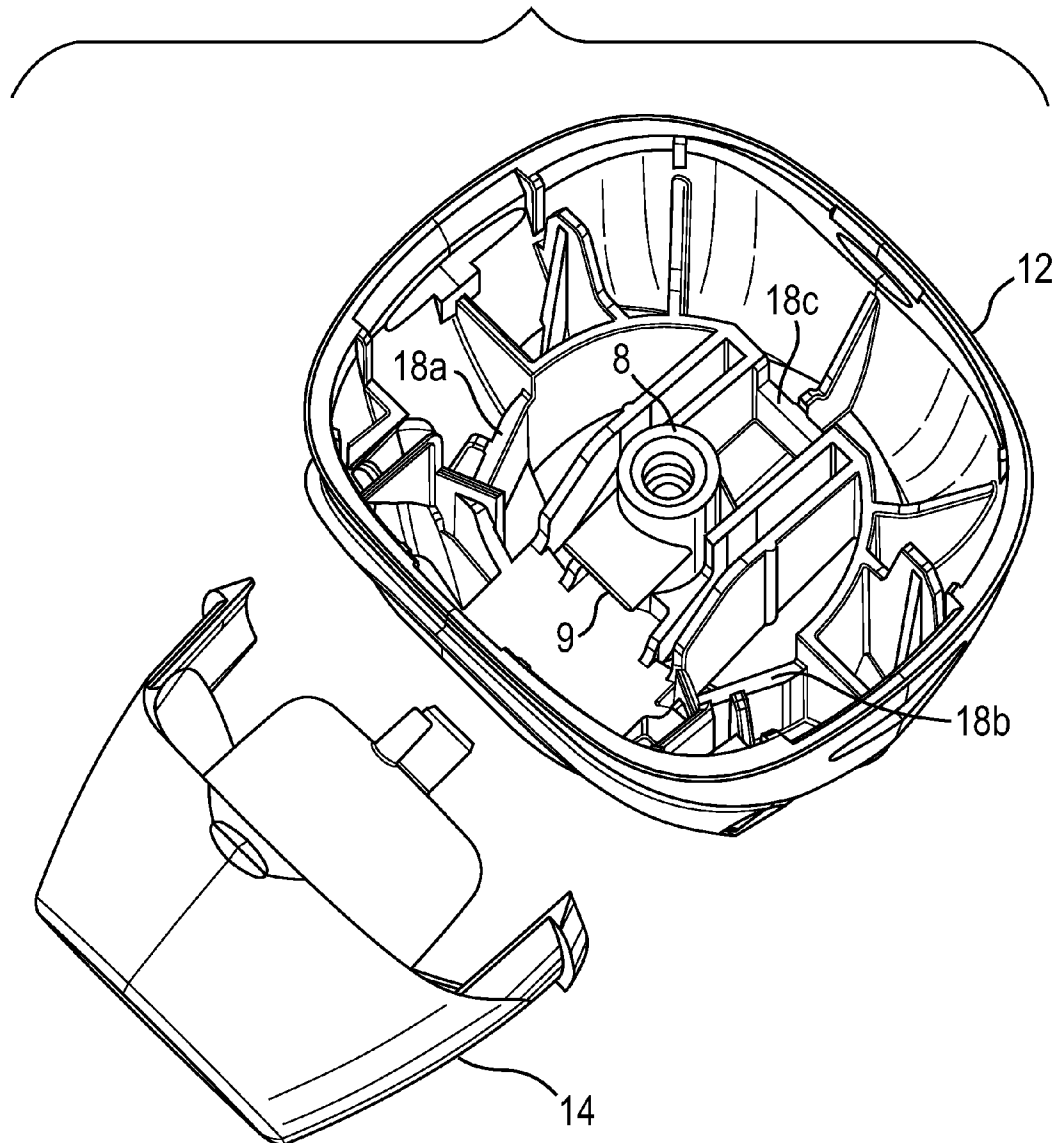


FIG. 29a

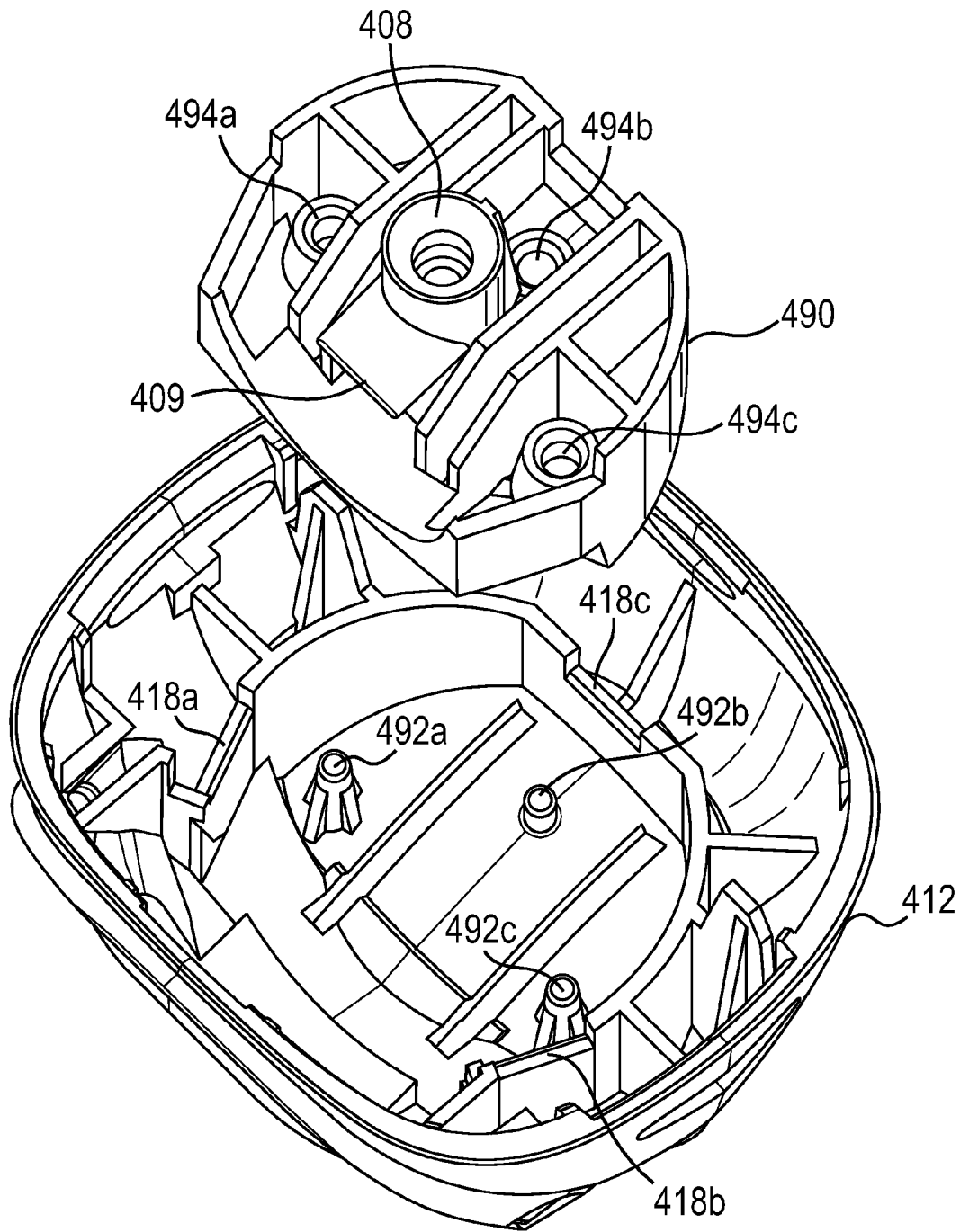


FIG. 29b

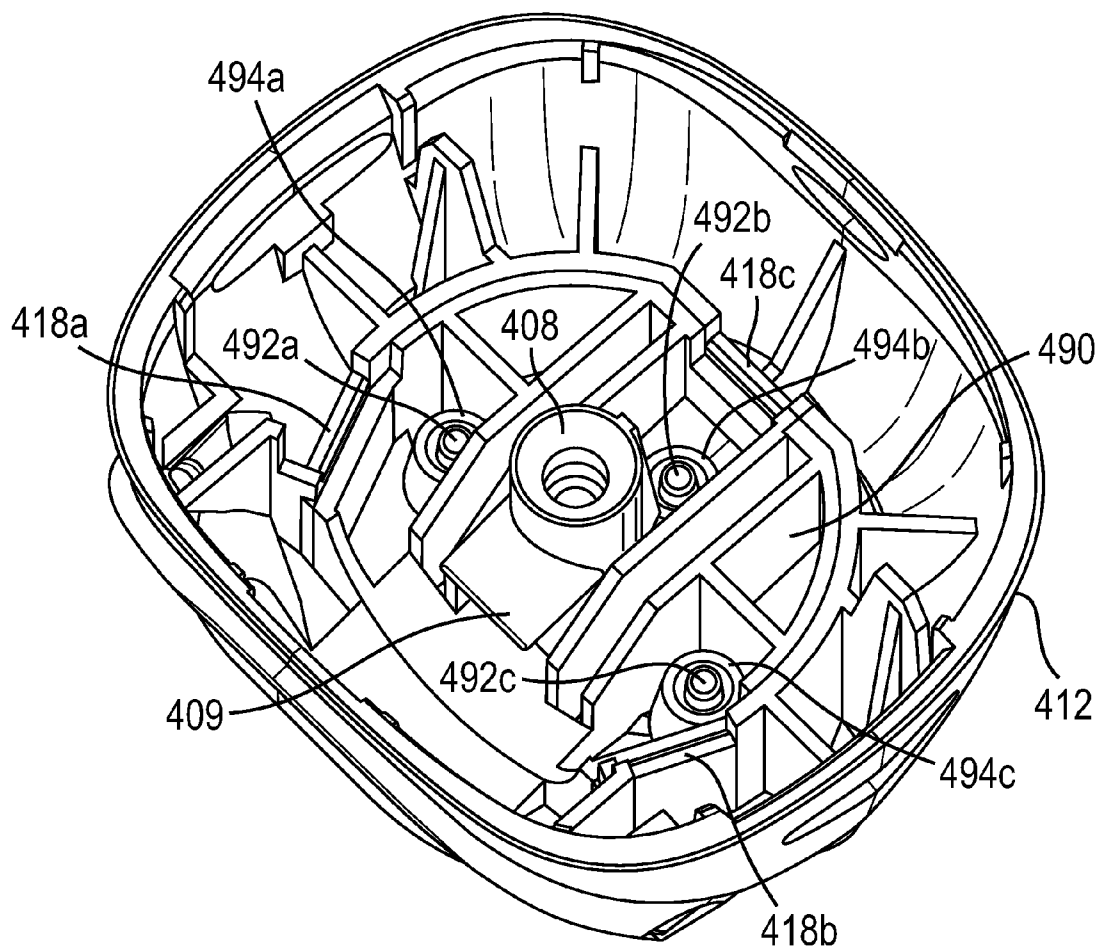


FIG. 30a

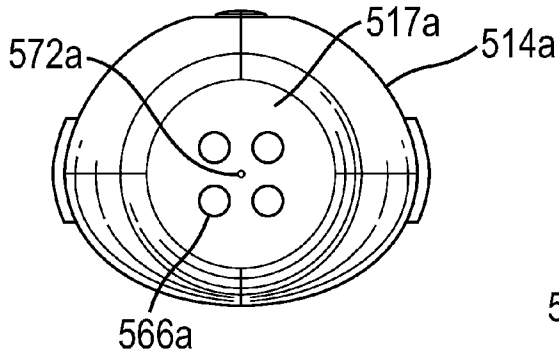


FIG. 30b

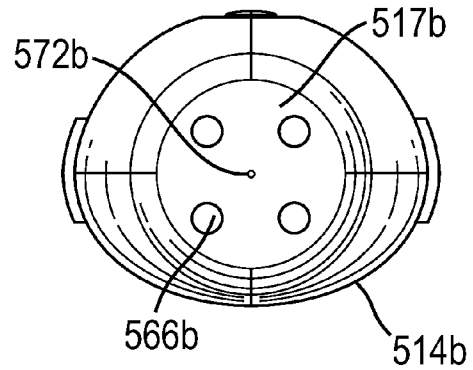


FIG. 30c

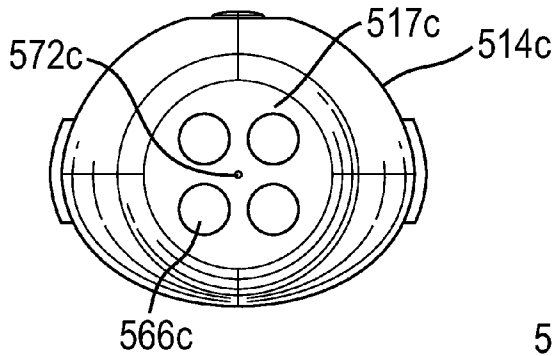


FIG. 30d

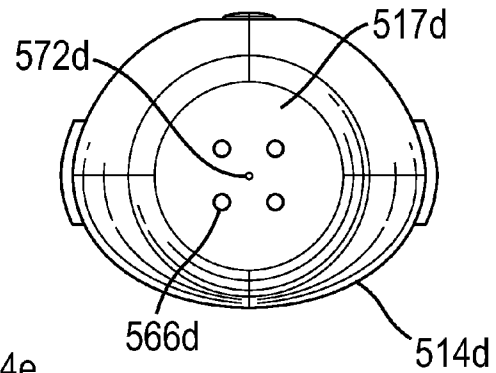


FIG. 30e

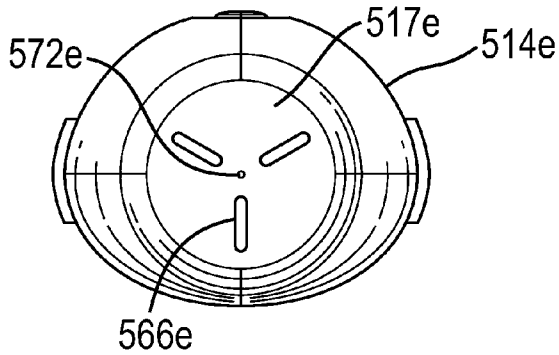


FIG. 30f

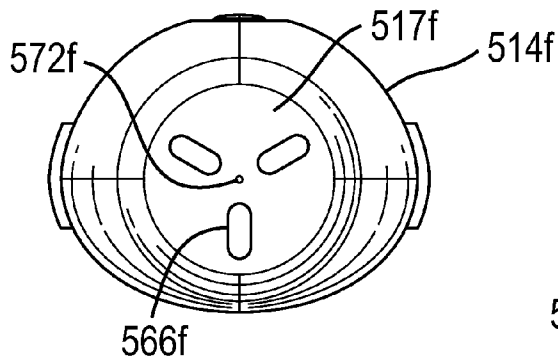


FIG. 30g

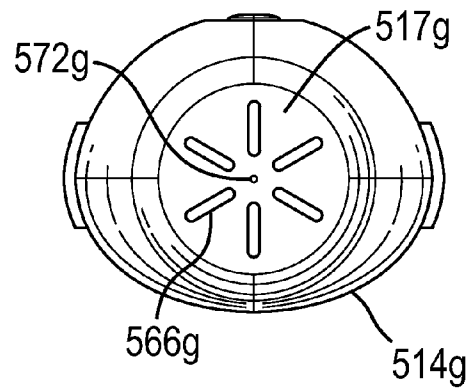


FIG. 30h

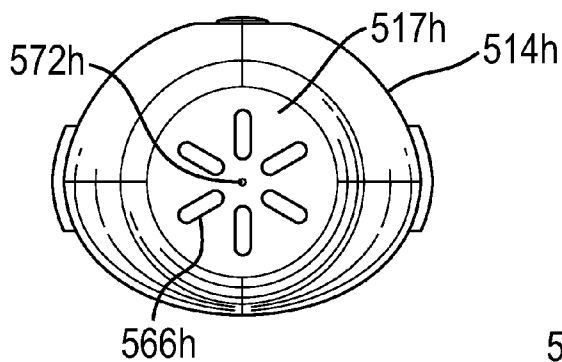


FIG. 30i

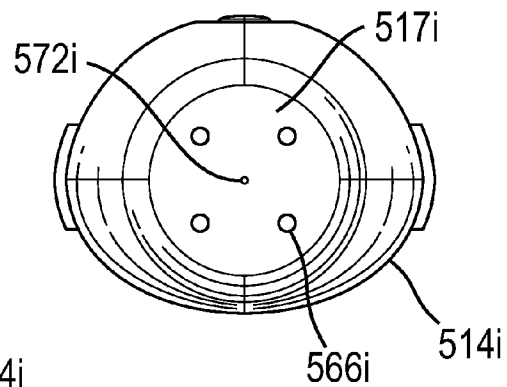


FIG. 30j

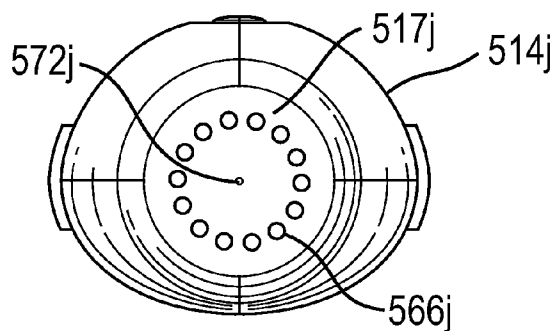


FIG. 30k

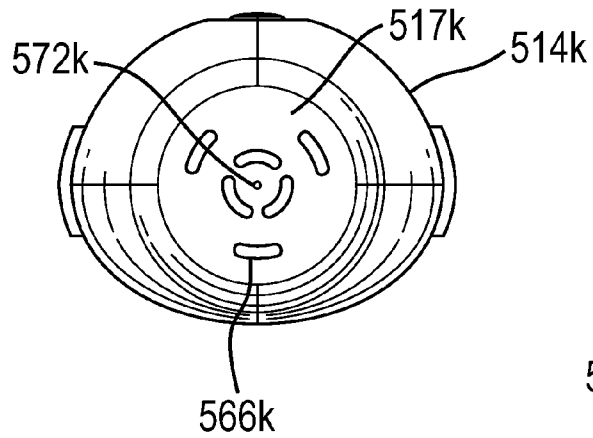


FIG. 30l

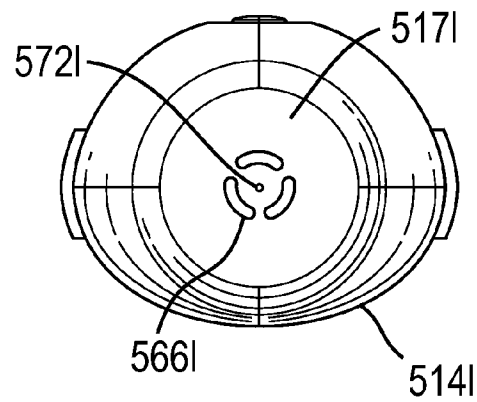


FIG. 30m

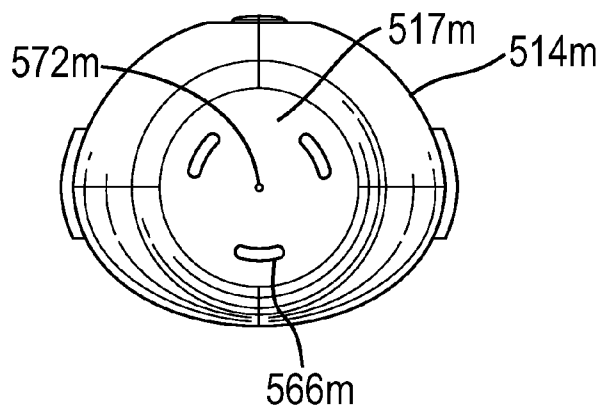
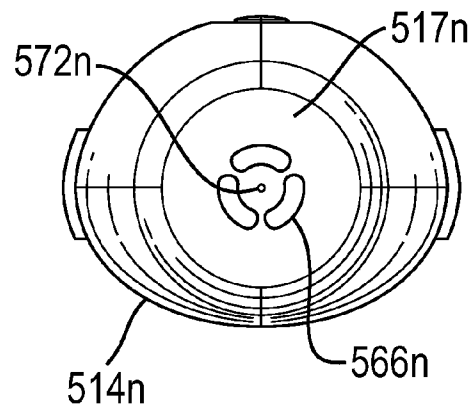


FIG. 30n



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**DRUG DISPENSER**

**[0001]** The present application claims priority from U.S. Provisional Application No. 60/823,141, filed 22 Aug. 2006, incorporated herein by reference in its entirety.

**[0002]** The disclosures of the following U.S. Provisional Applications are also incorporated herein by reference in their entirety: U.S. Provisional Application Nos. 60/823,134, 60/823,139, 60/823,143, 60/823,146, 60/823,151 and 60/823,154, all filed on 22 Aug. 2006; U.S. Provisional Application No. 60/894,537 filed on 13 Mar. 2007; and U.S. Provisional Application No. \_\_\_\_\_ entitled DRUG DISPENSER (Attorney Docket PB62118P1) and U.S. Provisional Application No. \_\_\_\_\_ entitled DRUG DISPENSER (Attorney Docket No. PB62540P) simultaneously filed herewith.

**[0003]** The disclosures of the International (PCT). Patent Applications simultaneously filed herewith, under Attorney Docket Nos PB61515, PB61970, PB62087, PB62088, PB62089 and PR61448, which designate the United States of America and claim priority from the aforementioned U.S. Provisional Application Nos. 60/823,134 60/823,139 60/823,143, 60/823,146, 60/823,151 and 60/523,154, are all also incorporated herein by reference in their entirety:

**[0004]** The present invention relates to a drug dispenser and in particular to a drug dispenser for delivering metered doses of aerosol or fluid drug formulation and adapted for use as an oral or nasal inhaler.

**[0005]** It is known to provide an actuator for an inhaler (e.g. a metered dose inhaler (MDI)) for delivering drug by inhalation, which actuator comprises a housing arranged for receipt of a container that contains drug formulation to be dispensed. The container typically comprises a body, which includes a base and a head, and a discharge mechanism (e.g. a valve or pump) which extends from the body and from which drug is in use discharged upon actuation thereof. The actuator also comprises an outlet, which is arranged for receipt by the mouth or nose of a user and through which a user in use inhales. The actuator further comprises a discharge assembly, which provides for delivery of drug through the outlet, wherein the discharge assembly typically comprises a discharge block, which receives the discharge mechanism of the container.

**[0006]** It is also known to provide an inhaler, in which a drug dose is dispensed to the patient via an outlet upon the application of a force by a user to an actuating lever or similar finger operable member provided to the housing. Typically, displacement of the actuating lever is arranged to transfer actuating force to the discharge mechanism provided to the drug container, which results in discharge of a drug dose. Such inhalers may be arranged to dispense a single dose or may alternatively be arranged with a reservoir containing several doses to be dispensed.

**[0007]** In conventional metered dose inhalers (MDIs) the housing is generally open to the environment. Typically, the base of the drug canister is arranged to protrude from an opening provided at the top of the actuator. This arrangement is designed to facilitate user access to the base of the canister for actuation of the inhaler by a user's finger and thumb motion which results in depression of the canister against a discharge block of the actuator housing and hence, firing thereof.

**[0008]** Applicant realizes that where an inhaler is instead arranged for actuation in response to user-applied force to an actuating lever or similar finger operable member provided to the housing it is not necessary that the housing is generally open to the environment. Indeed, it is considered advantageous from a hygiene standpoint to 'close off from the environment that part of the housing, which generally houses the drug container and discharge assembly. This generally 'closed off form can minimize undesirable ingress of foreign bodies (e.g. dirt particles), which might otherwise contaminate those working parts housed within the now 'closed off housing.

**[0009]** For effective operation of the inhaler it is desirable that one or more air inlets be provided to the housing, which air inlets allow air to be drawn into the housing (and desirably past the discharge mechanism of the container and discharge assembly) in response to the patient inhalation through an outlet (e.g. mouthpiece or nosepiece) of the inhaler. For optimal hygiene such air passage into the housing should only be enabled during use of the device and otherwise, the housing remains generally 'closed off from the environment.

**[0010]** Applicant therefore proposes an inhaler housing, in which is defined an aperture through which an actuating lever or other finger operable member at least in part protrudes. The finger operable member is moveable from a rest position in which the finger operable member acts to block off that aperture to an actuating position in which the aperture is unblocked and through which air may be drawn into the housing in response to patient inhalation through the outlet. Thus, both hygiene and effective operability requirements are provided for.

**[0011]** It is an aim of this invention to provide a drug dispenser that provides for effective operability and hygienic storage of a drug container thereof.

**[0012]** According to a first aspect of the invention there is provided a drug dispenser device according to claim 1 hereof.

**[0013]** There is provided a drug dispenser device for dispensing of a drug formulation to a patient by the inhaled route.

**[0014]** The drug dispenser device comprises a housing, which defines a first chamber and which is suitable for wholly or partly housing some or all of the parts of the dispenser device. The housing may have any suitable form but is suitably sized and shaped for ready accommodation by the hand of a patient. In particular, the housing is sized and shaped to enable one-handed operation of the dispenser device.

**[0015]** In preferred embodiments, the first chamber of the housing is essentially 'closed off other than for the (i) the discharge orifice of the discharge block, which allows for flow of discharged drug (e.g. aerolised form) from the discharge channel of the drug discharge device to the second chamber and thence to the outlet; and/or (ii) at least one further opening between the first chamber and second chamber to allow for air flow therebetween in response to patient inhalation through the outlet; and (iii) the selectively blocked off aperture, through which the at least one finger operable member protrudes. This generally 'closed off form of the first chamber is desirable from the standpoint of minimizing undesirable ingress of foreign bodies (e.g. dirt particles and other debris), which might otherwise contaminate the working parts of the drug dispenser device housed within the first chamber.



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**[0016]** Extending from the housing and defining a second open chamber, there is provided an outlet for insertion into a body cavity of a patient. Where the patient body cavity is the mouth of a patient, the outlet is generally shaped to define a mouthpiece. Where the patient body cavity is the nose of a patient, the outlet is generally shaped in nozzle form for receipt by a nostril of the patient. Thus, the part of the outlet, which allows for dispensed drug and/or air flow to the mouth or nose of the patient, also defines the principal opening of the 'open' form of the second chamber.

**[0017]** In embodiments, the outlet includes at least one air flow path which provides for a substantially annular air flow at an inner peripheral surface of the outlet on inhalation by the patient through the outlet, such as to provide a sheathing air flow to discharged drug (e.g. aerosolised form) when delivered from the discharge block orifice. In embodiments, a circular arrangement of plural air flow paths is provided.

**[0018]** In embodiments, the outlet is provided with a removeable protective cover such as a mouthpiece cover or nozzle cover.

**[0019]** Provided to the first chamber of the housing, there is a discharge block defining a discharge block orifice.

**[0020]** In embodiments, the discharge block comprises, as a separately-formed component, a discharge outlet which fluidly connects to the discharge block orifice of the discharge block and includes a discharge outlet orifice from which drug is in use, delivered.

**[0021]** The discharge outlet is in embodiments, integrally formed with or coupled to the outlet. In embodiments, the outlet comprises an external section which is configured to be gripped in the lips of the user and defines an open end through which drug is in use delivered and an internal section which defines a rear section to which the discharge outlet couples.

**[0022]** In embodiments, at least a rear section of the discharge outlet has an increasing internal dimension in a direction away from the discharge block. In one embodiment, the discharge outlet defines an essentially cone-shaped interior. In another embodiment, the discharge outlet defines an essentially an essentially bucket-shaped interior.

**[0023]** In embodiments, the discharge block includes a laterally-directed cavity which receives the discharge outlet. In embodiments, the discharge outlet is captively disposed in the laterally-directed cavity. The discharge outlet is suitably held captive in the laterally-directed cavity by any suitable joining or sealing method such as by use of a press-fit or snap-fit method; by use of a clip engaging mechanism; by use of over-welding; or by use of heat-staking. In embodiments, the discharge outlet is a snap-fit in the laterally-directed cavity.

**[0024]** In embodiments, the laterally-directed cavity includes a recess and the discharge outlet includes a projection which is captively engaged in the recess. In embodiments, the discharge outlet is an interference fit in the laterally-directed cavity.

**[0025]** In embodiments, the discharge outlet includes a delivery channel which is fluidly connected to the discharge outlet orifice and narrows towards the same. In one embodiment, the delivery channel has arcuate wall sections. In another embodiment, the delivery channel has substantially straight wall sections.

**[0026]** In embodiments, a sheathing air flow path at the outlet is enabled by the provision of air inlets to the discharge outlet. Where the discharge outlet is essentially bucket-shaped it has been found to be preferable that the air inlets are provided to the base of the bucket.

**[0027]** In embodiments, the annular air flow is in a direction away from the discharge block orifice. In embodiments, the outlet includes a plurality of air flow paths which together provide for the substantially annular air flow at the inner peripheral surface of the outlet.

**[0028]** Receivable within the first chamber and movement within the first chamber, there is provided, a drug discharge device. In embodiments, the drug discharge device is enclosed by the housing (i.e. enclosed within the first chamber). The drug discharge device has a longitudinal axis and comprises a container for storing a drug formulation to be dispensed. In embodiments, the container adopts a generally cylindrical form and the longitudinal axis is defined by the central axis of the cylinder. The container is suitably arranged to have a neck at one end.

**[0029]** The container is provided with a discharge mechanism, which communicates with a discharge channel extending from the container. The discharge channel is receivable by the discharge block to enable discharge of said drug formulation via the discharge block orifice to the outlet. In embodiments, the discharge channel extends out from a neck of the container.

**[0030]** Typically, the discharge mechanism is provided with spring mechanism (or other biasing mechanism) that provides a degree of bias that must be overcome in order to allow discharge of drug from the discharge mechanism. Typically, that spring mechanism also acts as a return mechanism to assist with return the discharge mechanism to its rest state after firing thereof.

**[0031]** It will be appreciated that the shape and form of the discharge channel will be matched to that of the discharge block for effective receipt thereby. In embodiments, the discharge channel is received by a cavity or passage provided to the discharge block of the housing, which cavity or passage enables communication with the discharge block orifice and thence with the outlet for dispensing of discharged drug to a patient.

**[0032]** In one aspect, where the discharge channel is the valve stem of a valved aerosol canister, the valve stem is received within a discharge block in the form of a stem block provided to the housing, which stem block includes a passage which acts such as to channel discharged aerosolized drug from the valve stem to the outlet.

**[0033]** In another aspect, where the discharge channel is the discharge tube of a fluid pump discharge device, the discharge tube is received within a discharge block in the form of a discharge tube block provided to the housing, which discharge tube block includes a passage which acts such as to guide discharged fluid drug from the discharge tube to the outlet.

**[0034]** In one aspect, the drug discharge device is suitable for dispensing aerosolized drug and thus, generally comprises an aerosol canister provided with a discharge valve of the type well-known for use in metered dose inhaler (MDI) type drug dispensers. The canister is generally formed of metal (e.g. aluminium). The valve generally includes a return spring such that once the valve has been fired it is returned to an 'at rest' position ready for subsequent firing thereof.

**[0035]** In a metered dose inhaler (MDI) the discharge device is for dispensing drug in aerosol form, wherein the drug is comprised in an aerosol container suitable for containing a propellant-based aerosol drug formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, which acts as the discharge mecha-



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nism for release of the aerosol form drug formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of drug upon each actuation by means of the valve, which can be opened by compressing the valved aerosol container, for instance by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

**[0036]** Where the drug container is an aerosol container, the valve typically comprises a valve body having an inlet port through which a drug aerosol formulation may enter said valve body, an outlet port through which the aerosol may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

**[0037]** The valve may be a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by the sealing ring a valve stem having a dispensing passage, the valve stem being slidably movable within the ring from a valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via the dispensing passage.

**[0038]** Typically, the valve is a metering valve. The metering volumes are typically from 10 to 100 such as 25  $\mu\text{l}$ , 50  $\mu\text{l}$  or 63  $\mu\text{l}$ . In embodiments, the valve body defines a metering chamber for metering an amount of drug formulation and an open/close mechanism by means of which the flow through the inlet port to the metering chamber is controllable. In preferred embodiments, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of drug formulation into the metering chamber.

**[0039]** The valve may also comprise a 'free flow aerosol valve' having a chamber and a valve stem extending into the chamber and movable relative to the chamber between dispensing and non-dispensing positions. The valve stem has a configuration and the chamber has an internal configuration such that a metered volume is defined therebetween and such that during movement between its non-dispensing and dispensing positions the valve stem sequentially: (i) allows free flow of aerosol formulation into the chamber, (ii) defines a closed metered volume for

pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and (iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with an outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation.

**[0040]** Suitably any of the inner parts of the valve (e.g. those which in use, will contact the drug formulation) are coated with material (e.g. fluoropolymer material) that reduces the tendency of drug to adhere thereto. Suitable fluoropolymer materials include polytetrafluoroethylene (PTFE) and fluoroethylene propylene (FEP). Any movable parts may also have coatings applied thereto, which enhance their desired movement characteristics. Frictional coatings may therefore be applied to enhance frictional contact and lubricants used to reduce frictional contact as necessary.

**[0041]** In another aspect, the drug discharge device is a fluid discharge device suitable for dispensing of fluid drug formulation (e.g. non-pressurised/propellant-free) and thus, generally comprises a fluid container provided with a compression

pump. Such pumped discharge devices are most commonly used in dispensers for dispensing fluid form drug for nasal delivery.

**[0042]** A suitable fluid discharge device comprises a container for storing a fluid to be dispensed having a neck at one end, a compression pump having a suction inlet located within the container and a discharge tube extending out from the neck of the container for transferring said fluid from the pump. The pump generally includes a return spring such that once the pump has been fired it is returned to an 'at rest' position ready for subsequent firing thereof.

**[0043]** A suitable pre-compression pump would be a VP3, VP7 or modifications, model manufactured by Valois SA. Typically, such pre-compression pumps are typically used with a bottle (glass or plastic) container capable of holding 8-50 ml of a formulation. Each spray will typically deliver 50-100  $\mu\text{l}$  of such a formulation and the device is therefore capable of providing at least 100 metered doses.

**[0044]** There is provided to the housing, at least one finger operable member moveable to apply a force directly or indirectly to the drug discharge device for movement of the drug discharge device along the longitudinal axis towards the discharge block to actuate the discharge mechanism. In preferred embodiments, the at least one finger operable member is moveable transversely with respect to the longitudinal axis of the drug discharge device.

**[0045]** The at least one finger operable member may be arranged to apply a force either directly or indirectly to the drug discharge device for actuation thereof. Where force is applied directly, a portion of the at least one finger operable member suitably engages the base of the container of the drug discharge device to push the container down in actuating fashion. Described hereinafter are other mechanisms including stored energy mechanisms, in which force is applied indirectly to the drug discharge device through one or more actuating mechanism parts.

**[0046]** The term at least one finger operable member is meant to encompass such members operable by action of the finger or thumb, or combinations thereof of a typical user (e.g. an adult or child patient). In embodiments, at least part of the at least one finger operable member is ergonomically shaped to assist interaction of the patient's finger and/or thumb therewith. Thus, in embodiments the at least one finger operable member may be shaped for ease of patient finger or thumb contact and/or be provided with surface features and/or other detailing that facilitates the desired interaction.

**[0047]** In embodiments, the at least one finger operable member is arranged to apply mechanical advantage. That is to say, the at least one finger operable member applies mechanical advantage to the user force to adjust (generally, to enhance or smooth) the force experienced by the transfer element. The mechanical advantage may in one aspect, be provided in either a uniform manner such as by a constant mechanical advantage enhancement, for example by a ratio of from 1.5:1 to 10:1 (enhanced force:initial force), more typically from 2:1 to 5:1. In another aspect, the mechanical advantage is applied in a non-constant manner such as progressive

increase or progressive decrease of mechanical advantage over the applied force cycle. The exact profile of mechanical advantage variation may be readily determined by reference to the desired dispensing performance of the dispenser device.

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[0048] In embodiments, the at least one finger operable member has a form, which naturally gives rise to mechanical advantage such as a lever.

[0049] In preferred embodiments, the at least one finger operable member comprises of at least one lever pivotally connected to part of the housing and arranged to urge the discharge device towards the discharge block when the or each lever is moved by a user.

[0050] In one preferred aspect, there are two opposing levers, each of which pivotally connect to part of the housing and may be arranged to transfer force directly or indirectly to the drug discharge device for movement of the drug discharge device along the longitudinal axis when the two levers are squeezed together by a user.

[0051] In one aspect, the movement of the two opposing levers is coupled, which coupling acts to wholly or partly compensate for uneven force being applied in use, by a patient to one lever as applied to the other lever. Any suitable coupling mechanism may be employed. In one aspect, the two opposing levers are provided with meshing teeth, which teeth are arranged to mesh together thereby providing a coupling action. Such coupling provides the further advantage when the opposing levers are actuated (e.g. by squeezing together) an equivalent-sized opening is unblocked (i.e. opened-up) about either lever, thereby providing for more even (i.e. symmetric) airflow through the device when a patient inhales therethrough.

[0052] In embodiments, the or each lever is pivotally supported at a lower end within the housing. By 'at a lower end within the housing' it is generally meant at that end of the housing which in normal use of the drug dispenser device by a patient is lowermost.

[0053] The use of a lower end pivoted lever configuration has the advantage that a long lever can be used thereby maximising the mechanical ratio between the input force and the force applied to actuate the drug discharge device. In addition the use of a lever pivotally supported at its lower end is ergonomically more efficient than using a lever pivotally supported at an upper end due to the fact that a user will normally grasp the dispenser device with their thumb positioned close to the end of the lever. With a lever pivotally supported at an upper end (again, relative to the normal 'in use' configuration) the location of a patient's thumb is close to the position about which the lever pivots and hence the maximum leverage is not obtained.

[0054] The housing further defines an aperture through which the at least one finger operable member at least in part protrudes, thereby making the at least one finger operable member accessible for finger/thumb actuation by a user. The protruding part of the at least one finger operable member is suitably shaped for finger and/or thumb interaction and may thus be provided with friction and/or gripping features to facilitate finger/thumb interaction.

[0055] Where more than one finger operable member (e.g. plural levers) is present, each is typically associated with an aperture through which at least part of that finger operable member protrudes. In embodiments, the or each aperture for the or each finger operable member is the sole (intended) entry point for airflow into the housing on patient inhalation at the outlet.

[0056] The at least one finger operable member is moveable from a rest position in which the at least one finger operable member acts to block off said aperture to an actuating position

in which the aperture is unblocked and through which air may be drawn into the housing in response to patient inhalation through the outlet.

[0057] In the rest position, the aperture is blocked off. By 'blocked off' it is meant that the aperture is essentially closed, particularly with the intention of blocking accessing to foreign bodies (e.g. dirt particles and other debris). An air-tight seal does not need to be formed, although in preferred embodiments the degree of blocking off is sufficient to at least impede or restrict air flow therethrough. In embodiments, a small gap (e.g. 0.5 mm all round) exists between the aperture of the housing and the at least one finger operable member. Desirably, in the rest position, the at least one finger operable member and the housing do not 'pinch' or 'jam' together. Such 'pinching' or 'jamming' interaction could otherwise affect the finger/thumb assisted movement of the at least one finger operable member which is required for operation of the device.

[0058] In embodiments, the at least one finger operable member is biased towards its resting position (i.e. with apertures blocked off) by a suitable biasing mechanism provided to the dispenser device. In embodiments the biasing mechanism is provided as (e.g. 'doubles up' as) a component of an actuating mechanism for actuating the container.

[0059] In the actuating position, the aperture is unblocked and air may thus, be drawn into the housing (i.e. the first chamber thereof and thence, to other parts thereof) in response to patient inhalation through the outlet.

[0060] In embodiments, the actuation mechanism for actuating the drug dispenser device herein comprises:

(f) connecting to the container, a container collar that engages the container;

(g) connecting to said container collar and moveable with respect thereto along the longitudinal axis of the drug discharge device, a transfer element, said transfer element including an actuating portion, wherein the at least one finger operable member is moveable to apply a force to said actuating portion of said transfer element to move the transfer element along the longitudinal axis in a first direction;

(h) connecting the container collar with the transfer element, a biasing mechanism to store biasing energy on moving the transfer element along the longitudinal axis in the first direction; and

(i) provided to the container collar, a pre-load mechanism to prevent transfer of said biasing energy to the container collar to move said container along the longitudinal axis in the first direction to actuate the discharge mechanism until a predetermined threshold force is overcome.

[0061] In embodiments, there is provided connecting to the container, a container collar that engages the container. The container collar is therefore suitably in essentially fixed relationship with (i.e. it fixes to) the container. In embodiments, the container collar engages (e.g. in essentially fixed relationship) with a neck of the container.

[0062] The container collar may engage with the (e.g. neck of the) container by any suitable means of permanent or temporary engagement including a snap-fit engagement mechanism. Preferably, as in the illustrated embodiments hereinafter, the container collar is permanently connected to the container through use of a split-ring collar as described in U.S. patent application Ser. Nos. 10/110,611 (WO-A-01/28887) and US-A-2006/0082039.

[0063] In embodiments, the at least one finger operable member is arranged for direct engagement with the container

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collar to apply actuating force to the container collar to push or pull the container down in actuating fashion.

**[0064]** In other embodiments, there is further provided connecting (via a biasing mechanism as later described) to the container collar and moveable with respect thereto along the longitudinal axis of the drug discharge device, a transfer element. The transfer element may have any suitable form but preferably comprises an extension collar that is sized and shaped for receipt by the container and arranged in suitable fashion relative to the container collar. In one aspect, the extension collar is sized and shaped for receipt around (i.e. external to) the container collar.

**[0065]** In these other embodiments, the transfer element includes an actuating portion and the at least one finger operable member is moveable to apply a force to the actuating portion of the transfer element to move the transfer element along the longitudinal axis in the first direction. The actuating portion is shaped for interaction with the at

least one finger operable member, and may take any form that facilitates and accommodates that interaction including abutment (e.g. flange or shelf), rack and pinion gear and indent forms. In embodiments, the actuating portion defines an abutment surface. Similarly, the at least one finger operable member is suitably shaped for direct interaction with the actuating portion, and may take any form that facilitates and accommodates that direct interaction including abutment and indent forms. In embodiments, the at least one finger operable member defines a cam surface arranged for interaction with the actuating portion of the transfer element.

**[0066]** Optionally, there is provided to drug dispenser device a locking mechanism for reversibly locking/unlocking the movement of the at least one finger operable member and/or any container collar. The purpose of the locking mechanism is to prevent unintended movement of the at least one finger operable member and/or container collar and hence, to prevent unintended actuation of the dispenser device.

**[0067]** In embodiments, the locking mechanism comprises a locking element comprising any suitable limb, protrusion, or abutment which acts such as to interfere with the unintended movement of the at least one finger operable member and/or container collar. Such unintended movement may for example, arise as a result of patient misuse of the dispenser device or during transport of the device (e.g. when carried in the pocket or bag of a patient).

**[0068]** In one aspect, the locking mechanism is provided to a removeable cover for the outlet (e.g. mouthpiece or nozzle cover). Thus, in use the patient would remove the outlet cover thereby simultaneously revealing the outlet and unlocking the locking mechanism. Conversely, after the use the outlet cover is replaced to again lock the at least one finger operable member and/or container collar. In alternative aspects, the locking mechanism may comprise an integral part of the removeable cover or by provided as a fixed add-on thereto or be provided as a moveable (e.g. rotatable or translatable) add-on thereto.

**[0069]** In one aspect, the locking mechanism is arranged to prevent unintended movement of the container collar and hence, firing of the discharge mechanism, but does not impede the movement of the at least one finger operable member and/or of the transfer element. Thus, when the container collar is in its locked state (i.e. the locking mechanism is performing its locking function) the at least one finger operable member (e.g. levers) may still be moved and that

movement transfer energy via the biasing mechanism to move the transfer element, but all movement of the container collar is prevented. This form of locking arrangement has the advantage that unintended force applied to the finger-operable (e.g. levers) allows for travel thereof without damage thereto or to the device as a whole, but without any actuation of the dispenser device (e.g. by firing of the discharge mechanism).

**[0070]** In embodiments, the container collar is provided at its underside with one or more (e.g. two) downward protrusions and the mouthpiece is provided with a locking mechanism in the form of one or more interference elements. In embodiments, the interference element(s) is P-shaped and joined to the mouthpiece by means of a suitable hinge (e.g. living hinge) about which the interference element(s) may rotate. In an embodiment, there are two interference elements joined together by a bridge element. When, the mouthpiece engages with the body of the dispenser device (i.e. in the mouthpiece-closed position) the interference element(s) abuts the downward protrusion(s) to thereby prevent (i.e. lock) any downward movement of the container collar. Unintended movement of the container collar and hence, unintended actuation of the dispenser device (i.e. firing of the discharge mechanism) is hence prevented. In embodiments, however the at least one finger operable member and transfer element are free to move, even when the container collar is in its locked state.

**[0071]** One particular locking mechanism, in which one or more rotatable interference elements are provided to the mouthpiece, is described in Applicant's co-pending PCT Patent Application No. WO-A-2007/028,992 which claims priority from UK patent application no. 0518355, each incorporated herein by reference.

**[0072]** In embodiments, there is further provided a biasing mechanism which acts such as connect the container collar to the transfer element. The biasing mechanism acts to store biasing energy on moving the transfer element relative to the container collar along the longitudinal axis in the first direction.

**[0073]** In embodiments, the biasing mechanism comprises one or more springs or other resiliently compressible or expandable mechanical members for storing mechanical energy.

**[0074]** In preferred embodiments of this type, the biasing mechanism comprises an arrangement of two springs locating one on either side of the container collar (i.e. 180° radial spacing).

**[0075]** The Applicant realizes that for effective actuation of the discharge mechanism (e.g. valve or pump) of the drug discharge device any biasing mechanism should be capable of storing (and releasing) sufficient biasing energy to both overcome any pre-determined force of any pre-load mechanism and to actuate that discharge mechanism. Thus, for example where the discharge mechanism comprises a valve or pump having a return spring, the biasing mechanism should be capable of providing sufficient biasing energy to overcome that return spring to reliably fire the valve or pump.

**[0076]** The Applicant realizes that it is desirable that the actuating force, which is applied by the patient to the at least one finger operable member be kept to a minimum. Desirably also, the overall size of the device is kept relatively small (e.g. fits comfortably in the patient's hand) from both an ergonomics and aesthetics standpoint. Desirably also, the dispenser device is made of plastic components, although this brings



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with it the challenge that the mechanical strength of certain plastics reduces with time, particularly if they are left in a tensed state.

**[0077]** Thus, in embodiments the biasing mechanism is suitably arranged to provide an initial high biasing tension (e.g. to be equal to or greater than the force required to actuate a return spring of the valve or pump, but necessarily also less than that of a pre-determined threshold force of any pre-load mechanism), and further to have a low spring rate (i.e. the tension therein increase by only a low rate as the biasing mechanism is moved in response to user-actuation of the at least one finger operable member). Applicant realizes that it can be difficult to achieve this with a compression spring since it would require making a spring with a low spring rate then compressing it a given distance to achieve the initial high biasing tension, and then assembling it into the device. It would therefore always be putting a load upon any plastic components of the device.

**[0078]** Thus, in embodiments the biasing mechanism comprises one or more extension springs.

**[0079]** In embodiments, the degree of extension of the or each extension spring is greater than that of the degree of spring extension required to overcome any return spring (e.g. valve or pump return spring) of the discharge mechanism to fire that discharge mechanism.

**[0080]** In preferred embodiments, the extension springs have a closed coil form, which suitably defines an initial biasing tension in its 'at rest' state. In embodiments, that initial biasing tension provided by the one or more extension springs in combination is just below (e.g. from 1 to 15N, such as from 3 to 10N below) that of the pre-determined threshold force of the pre-load mechanism.

**[0081]** In embodiments, the one or more extension springs define a low spring rate. That is to say extension thereof does not require undue user force to be applied. This is advantageous in that extension thereof in response to user actuation of the at least one finger operable member does not thereby, put undue strain on the user. In embodiments, the spring rate of the or each extension spring is in the range from 0.5 to 5 N/mm, such as from 1 to 3 N/mm.

**[0082]** In embodiments, there is further provided to the container collar, a pre-load mechanism to prevent transfer of biasing energy to the container collar to move said container along the longitudinal axis in the first direction to actuate the discharge mechanism until a pre-determined threshold force is overcome.

**[0083]** Thus, initially as the transfer element moves along the longitudinal axis in response to patient actuation of the at least one finger operable member the spacing (along the longitudinal axis) between the transfer element and the container collar (which does not move) increases and biasing energy builds up in the biasing mechanism. Once however, the pre-determined threshold force as defined by the pre-load mechanism is exceeded, the biasing energy is released and the container collar is thereby, drawn along the longitudinal axis and in the first direction, which action results in actuation of the discharge mechanism resulting in discharge of drug formulation through the discharge channel and to the outlet for delivery to the patient.

**[0084]** In other words, the pre-load mechanism acts such as to prevent actuation of the discharge mechanism of the drug discharge device until a pre-determined threshold force is applied to the at least one finger operable member. The pre-determined threshold force may thus, be thought of as a

'barrier' force which must first be overcome before the energy stored in the biasing mechanism may be released to actuate the discharge mechanism. In essence, the pre-load mechanism acts as a 'commitment' feature, which allows release of actuating energy to the dispensing mechanism only when the 'barrier' force has been exceeded.

**[0085]** The quantum of pre-determined force that is to be overcome before actuation of the discharge mechanism is enabled is selected according to various factors including the typical user profile, nature of the drug formulation and the desired discharge characteristics.

**[0086]** Typically, the pre-determined threshold force is in the range from 5 to 40N, more typically from 10 to 30N (e.g. 15N). That is to say, typically from 5 to 40N, more typically from 10 to 30N (e.g. 15N) of force must be applied to overcome the predetermined threshold before actuation of the discharge mechanism is enabled. Such

values tend to correspond to a force which prevents a suitable 'barrier force' to a weak, nondescript or unintended finger movement whilst readily being overcome by the determined finger (or thumb) action of a user. It will be appreciated that if the device is designed for use by a child, or elderly patient it may have a lower pre-determined force than that designed for adult usage.

**[0087]** In embodiments, the pre-load mechanism is interposed between the container collar and the housing.

**[0088]** In embodiments, the pre-load mechanism comprises one or more detents formed on the container collar for engagement with part of the housing, the or all of the detents being disengageable from the housing when the pre-determined threshold force is applied to the transfer element via the at least one finger operable member so as to allow the container collar to move along the longitudinal axis in such a way that the discharge mechanism is actuated.

**[0089]** In preferred embodiments, each detent comprises a flexible (e.g. resilient) support limb, such as a support leg, which engages (e.g. latches to) a step or abutment provided to the housing. When the pre-determined threshold force is overcome, the or each flexible support limb disengages from the step or abutment to allow the container collar to move along the longitudinal axis such that the discharge mechanism is actuated. In embodiments, the or each support limb is provided to the lower end of the container collar (i.e. that end which is closest to the outlet). An arrangement of from two to four (e.g. three) flexible support limbs is particularly preferred. Alternatively, the or each support limb may have a hinged or articulated form.

**[0090]** In embodiments, a guide mechanism is provided to the transfer element (e.g. extension collar) to guide the disengagement of the flexible support limb from its respective step or abutment on the housing. Preferably, such guide mechanism comprises a guide ramp, which interacts with a shaped head of each flexible support limb.

**[0091]** In embodiments, a reseal guide mechanism is provided to the transfer element (e.g. extension collar) to guide the re-engagement of the flexible support limb with its respective step or abutment on the housing. Preferably, such reseal guide mechanism comprises a reseal guide ramp, which interacts with a shaped reseal head of each flexible support limb.

**[0092]** In embodiments the 'disengagement' guide mechanism (e.g.) ramp interacts with an outer shaped head of each flexible support limb and the 're-engagement' reseal guide mechanism (e.g. ramp) interacts with an inner shaped reseal head of each flexible support limb.

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**[0093]** Alternatively, the pre-load mechanism may comprise of one or more detents formed on the housing for engagement with part of the container collar, the or all of the detents being disengageable from the container collar when the pre-determined threshold force is applied to the transfer element via the at least one finger operable member so as to allow the discharge mechanism to be actuated.

**[0094]** In embodiments, the drug dispenser herein includes an actuation counter. The actuation counter suitably includes a mechanism for registering and displaying dose count information to the patient. In embodiments, that dose count information relates to the number of doses of drug delivered from or remaining in the dispenser device. The information may be delayed in digital or analogue form, typically using standard count indicia (e.g. '999' to '000' indicia count display). Embodiments involving either 'counting up' or 'counting down' in increments are envisaged.

**[0095]** The pre-load mechanism herein acts such as prevent transfer of biasing energy to the container collar to actuate the actuation counter until a pre-determined threshold force is overcome. Thus, a count is registered by the actuation counter only in response to a user actuation that is sufficient to overcome the 'barrier' force provided by the pre-load mechanism and which thereby results in dispensing of a dose from the drug container.

**[0096]** In embodiments, the actuation counter is actuatable in response to movement of the container collar or of the container along the longitudinal axis in the first direction.

**[0097]** In embodiments, the actuation counter is actuatable in response to drive (e.g. engageable drive) interaction with a driver element provided to the container collar or container. The driver element may for example, take the form of a protrusion (e.g. tooth), an abutment, an indent or a slot provided to the container collar or container.

**[0098]** In embodiments, the actuation counter is actuatable in response to drive interaction with a driver element provided to a drive feature connecting to the container collar or container. The driver element may for example, take the form of a protrusion (e.g. tooth), an abutment, an indent or a slot provided to the drive feature. In embodiments, the drive feature comprises a plate connecting to the container collar.

**[0099]** The actuation counter may adopt any suitable form. The actuation counter is in embodiments sized and shaped for effective receipt by the housing of the drug dispenser. In embodiments, the actuation counter has the form described in Applicant's co-pending U.S. Provisional Application No. 60/894,537 filed on 13 Mar. 2007 or in U.S. Provisional Application No. \_\_\_\_\_ entitled DRUG DISPENSER (Attorney Docket No. PB62118P1) commonly owned and filed simultaneously herewith, both incorporated herein by reference in their entirety.

**[0100]** Embodiments are envisaged in which the drug discharge device is reversibly removable from the housing of the drug dispenser device. In such embodiments the drug dispenser device comprises a housing assembly and a drug discharge device receivable thereby.

**[0101]** According to a still further aspect of the present invention there is provided a kit of parts comprising a housing assembly as described above and a drug discharge device receivable thereby.

**[0102]** It is also envisaged that the housing assembly could be supplied as a separate item, into which a user or pharmacist later fits a suitable drug discharge device.

**[0103]** The drug dispenser device of the invention is suitably an inhaler, more suitably of the well-known "metered dose inhaler" (MDI) type, and yet more suitably a hand-held, hand-operable breath-coordinated MDI. In such a MDI, the patient manually actuates the MDI for release of the drug from the drug discharge device while concurrently inhaling at the outlet. Thus inhalation and actuation are coordinated. This is in distinction from breath-operated MDIs, where the inhalation event itself actuates the MDI so that no coordination is required.

**[0104]** Additional aspects and features of the present invention are set forth in the claims and in the description of exemplary embodiments of the present invention which now follow with reference to the accompanying Figures of drawings. Such exemplary embodiments may or may not be practiced mutually exclusive of each other, whereby each embodiment may incorporate one or more features of one or more of the other embodiments. It should be appreciated that the exemplary embodiments are set forth to illustrate the invention, and that the invention is not limited to these embodiments.

**[0105]** The invention will now be described further with reference to the accompanying drawing in which:—

**[0106]** FIG. 1 shows a perspective view of a hand-held, hand-operable, breath-coordinated drug dispenser device of the MDI type herein in the 'at rest' position;

**[0107]** FIG. 2 shows a perspective view of the drug dispenser device of FIG. 1 with upper front cover part, actuation counter, front plate, mouthpiece and mouthpiece cover removed and the lower front cover part shown in cut-away section, the device again being shown in the 'at rest' position;

**[0108]** FIGS. 3a to 3b show front views of the drug dispenser device of FIG. 1 with upper front cover part, actuation counter, front plate and mouthpiece cover removed and the left lower front cover part and left-side of mouthpiece shown in cut-away

section, the device respectively being shown in 'at rest' and first stage of actuation positions;

**[0109]** FIGS. 4a to 4c show front views of the drug dispenser device of FIG. 1 with upper front cover part, actuation counter, front plate, mouthpiece cover and left lever removed and the left lower front cover part and left-side of mouthpiece shown in cutaway section, the device respectively being shown in second, third and fourth stages of actuation positions;

**[0110]** FIG. 5 shows an exploded view from the front of part of the internal mechanism of the drug dispenser device of FIG. 1 with front plate removed;

**[0111]** FIG. 6 shows a schematic view of part of the internal mechanism of the drug dispenser device of FIG. 1 with front plate removed, and in particular, the 'interlock' mechanism provided to block actuation thereof when the mouthpiece is covered by the mouthpiece cover;

**[0112]** FIG. 7 shows a perspective view of the drug dispenser device of FIG. 1 with the mouthpiece cover removed from the mouthpiece and thus, in a 'ready to use' position;

**[0113]** FIG. 8 shows a perspective view of the drug dispenser device of FIG. 1 with the mouthpiece cover removed from the mouthpiece and the levers depressed and thus in the 'in use' position;

**[0114]** FIG. 9 illustrates a perspective view of a first half of the drug dispenser of FIG. 1 showing air flow into the housing in the 'in use' position thereof;

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[0115] FIG. 10 illustrates a perspective cut-away view of a second half of the drug dispenser device of FIG. 1 (with actuation counter and details of internal mechanism omitted) showing air flow through the chambers of the housing in the 'in use' position thereof;

[0116] FIG. 11 illustrates a perspective cut-away view of a second half of a drug dispenser device that is a slight variation of that drug dispenser device of FIG. 1 (with actuation counter and details of internal mechanism omitted) showing air flow through the inhaler body in the 'in use' position thereof;

[0117] FIG. 12 shows an exploded view of an actuation counter herein arranged for receipt within the front upper housing part of the first drug dispenser of FIG. 1 or second drug dispenser device of FIG. 11;

[0118] FIGS. 13a and 13b respectively show underside and top views of the actuation counter of FIG. 1;

[0119] FIGS. 14a and 14b show cut-away views of the actuation counter of FIG. 12 at respectively 'count 120' and 'count 119' positions;

[0120] FIGS. 15a and 15b respectively show cut-away views corresponding to FIGS. 14a and 14b of the actuation counter of FIG. 12 absent the decimals count wheel;

[0121] FIGS. 16a and 16b respectively show cut-away views corresponding to FIGS. 14a and 14b of the actuation counter of FIG. 12 absent the numerals count wheel;

[0122] FIGS. 17a and 17b show cut-away views of the actuation counter of FIG. 12 at respectively 'count\_0' and 'shuttered' positions;

[0123] FIGS. 18a and 18b respectively show cut-away views corresponding to FIGS. 17a and 17b of the actuation counter of FIG. 12 absent the numerals count wheel;

[0124] FIG. 19 shows a front view of the drug dispenser device of FIG. 1 with upper front cover part and actuation counter removed, the device being in the 'at rest' position;

[0125] FIG. 20 shows a perspective view of the drug dispenser device of FIG. 1 with the upper front cover part and actuation counter disposed therein shown detached from the remainder of the device, the device being shown in a 'at rest' position;

[0126] FIG. 21 shows a plan view of the inner side of the upper front cover part of the drug dispenser device of FIG. 1 and showing the actuation counter disposed therein;

[0127] FIGS. 22 and 23 show perspective views of a container collar part for use in an alternative internal mechanism for use with the drug dispenser device herein, as respectively shown in upright and inverted configurations;

[0128] FIGS. 24 and 25 respectively show perspective underside and top views of an extension collar part for use in an alternative internal mechanism for use with the drug dispenser device herein;

[0129] FIGS. 26a to 26c show perspective views of sequential steps in the assembly of an alternative internal mechanism for use with the drug dispenser device herein, and employing the container collar of FIGS. 22 and 23 and the extension collar of FIGS. 24 and 25;

[0130] FIGS. 27a to 27c show sectional side views of interaction of key parts of the container collar of FIGS. 22 and 23 with the extension collar of FIGS. 24 and 25 during sequential operational steps of the alternative mechanism assembled as shown in FIGS. 26a to 26c;

[0131] FIG. 28 shows a perspective view from above of the lower housing part and mouthpiece assembly (shown separated) of the drug dispenser device of FIG. 1;

[0132] FIGS. 29a and 29b show an alternative 'two part form' lower housing part, as respectively shown separated and as assembled, for use with the drug dispenser device of FIG. 1; and

[0133] FIGS. 30a to 30c respectively show front views of mouthpiece forms, which may be employed in the drug dispenser devices of FIG. 1 or 11 as an alternative to the mouthpieces thereof.

[0134] Turning now to the drawings, FIG. 1 shows a drug dispenser device 1 herein which is in the form of a hand-held, hand-operable, breath coordinated pressurised metered dose inhaler (MDI). This type of device requires a patient to coordinate their inhalation at a dispensing outlet of the device (in this embodiment, a mouthpiece 14) with manual actuation of the device so that the inhalation is coordinated with release of drug from the device so that drug is entrained by the inhalation airflow to the target location in the respiratory tract (in this case, the lungs) of the patient.

[0135] The device 1 comprises a housing defined in combination by front 10a and rear 10b upper housing parts and lower housing part 12, all of which are, in this embodiment, formed from plastic. It will be noted that the overall form of the housing is arranged for ease of receipt by a user's hand such that in general terms the rear of lower housing part 12 is received by the user's palm. Mouthpiece 14 (not visible in FIG. 1, but see FIG. 3a) is protected by removeable mouthpiece cover 16, and extends from the front of lower housing part 12 and is arranged in use, for insertion into the mouth of a patient for inhalation therethrough.

[0136] A ledge 13a, 13b is provided to the base of the lower housing part 12 such that the device may be arranged to 'stand upright' on the ledges 13a, 13b and mouthpiece cover 16, when cover 16 covers the mouthpiece 14. As will be understood from FIG. 7, when the cover 16 is moved to its 'mouthpiece uncovered' position, the device is able to 'stand upright' on the end face 16a of the cover 16 itself.

[0137] A viewing window 216 is provided to the front upper housing part 10a for viewing of count indicia displayed by a counter 201 locating within that part 10a and described in more detail hereinafter with reference to FIGS. 12 to 21.

[0138] Opposing levers 20a, 20b protrude from apertures 11a, 11b provided to the front 10a and rear 10b upper housing parts. The levers 20a, 20b are shaped such as to respectively accommodate the finger and thumb of a patient in use, thereby facilitating one-handed operation of the device.

[0139] FIG. 28 shows the lower housing part 12 and mouthpiece 14 (shown separated from each other, in this view) of the drug dispenser device of FIG. 1. Provided to the lower housing part 12 is stem block 8, which is arranged to receive valve stem 7 of an aerosol canister 5 (see also FIG. 2). The stem block 8 also includes a passage 9, which in use acts such as to guide discharged aerosolized drug from the valve stem 7 to the mouthpiece 14. Step portions 18a, 18b, 18c, the purpose of which will be described in more detail in the later description, are also provided.

[0140] FIGS. 29a and 29b show an alternative 'two part form' lower housing part 412, as respectively shown separated and as assembled, for use with the drug dispenser device of FIG. 1 as an alternative to the lower housing part 12 of FIG. 28. This two part form comprises lower housing part 412, which is arranged to receive separate stem block part 490. That separate stem block part 490 includes stem block 408 and stem block passage 409. As before, the lower housing part defines step portions 418a, 418b, 418c. During assembly the



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separate parts **412**, **490** are brought together and sockets **494a**, **494b**, **494c** on the stem block part **490** aligned with posts **492a**, **492b**, **492c** on the lower housing part. The parts **412**, **490** are then joined to each other by means of heat welding ('heat staking') at each respective post **492a**, **492b**, **492c** to socket **494a**, **494b**, **494c** mating point. Advantages of using the alternative 'two part form' lower housing part **412** and stem block part **490** assembly are that the precision features of the stem block part **490** are easier to produce and inspect. The stem block part **490** is generally made from a polymer selected for ease of drug delivery. The lower housing part **412** is in embodiments, formed of ABS.

[0141] Details of the inner workings of the device **1** of FIG. **1** may be appreciated by reference to FIG. **2**, in which the upper **10a** front housing part and mouthpiece

cover **16** have been removed. It will be seen that each opposing lever **20a**, **20b** pivotally connects to the upper housing part **10a**, **10b** by means of pivot connector **22a**, **22b**. The positioning of the pivotal connection is selected to facilitate the desired finger-thumb operability of the levers **20a**, **20b** by a squeezing movement. It will also be seen that the lower ends **21a**, **21b** of each lever **20a**, **20b** mesh together, thereby tending to the couple the motion of each respective lever **20a**, **20b** one to the other.

[0142] Although not shown, each lever **20a**, **20b** has a lower end **21a**, **21b** on either side thereof providing a generally U-shape to each lever **20a**, **20b**.

[0143] Provided to the housing, but largely obscured from view by container collar **30**, there is provided a drug discharge device, which takes the form of cylindrical valved aerosol canister **5** of the type commonly known for use in an MDI. A valve stem **7** of the drug discharge device is received within a stem block **8** provided to the housing, which stem block **8** includes a passage **9** which acts such as to guide discharged aerosolized drug from the valve stem to the mouthpiece **14**.

[0144] The levers **20a**, **20b** are arranged in the device such that the lower ends **21a**, **21b** of each lever **20a**, **20b** are disposed on opposing sides (front and rear) of the drug discharge device.

[0145] In this particular embodiment, and referring to FIG. **5**, the canister **5** has a body **6** made of metal, for instance of stainless steel or, more preferably, of aluminium or an aluminium alloy. The canister contains a pressurised drug aerosol formulation. The formulation comprises the drug (one or more drug actives) and a fluid propellant, and optionally one or more excipients and/or adjuvants. The drug is in solution or suspension in the formulation. The propellant is typically a CFC-free propellant, suitably a liquid propellant, and preferably is a HFA propellant, such as HFA-134a or HFA-227 or a combination thereof. The drug active(s) is typically of the type for use in treatment of a respiratory disease or condition, such as asthma or chronic obstructive pulmonary disease (COPD). The active(s) may also be for prophylaxis or palliation of a respiratory disease or condition.

[0146] The canister **5** may have its inner surface coated with a fluorocarbon polymer, optionally in a blend with a non-fluorocarbon polymer, such as a blend of polytetrafluoroethylene and polyethersulphone (PTFE-PES), as disclosed in U.S. Pat. Nos. 6,143,277; 6,511,653; 6,253,762; 6,532,955; and 6,546,928. This is particularly preferred if the drug is in suspension in the formulation, and especially if the suspension formulation is composed only, or substantially only, of the drug and HFA propellant.

[0147] The valve stem **7** forms part of a metering valve (not shown) mounted in the canister **5**, as will be understood by the skilled person in the art, and as commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bepak plc, UK (e.g. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser™). The metering chamber of the metering valve may be coated with a fluorinated polymer coating, such as formed from perfluoro-hexane, for instance by cold plasma polymerisation, as detailed in US-A-2003/0101993.

[0148] As may be further understood with reference also to FIG. **5**, which shows an exploded view of key parts of the internal mechanism, the container collar **30** permanently engages via split-ring collar **33** with the neck **5a** of the canister **5** such that the so-engaged parts are moveable together relative to the housing in a direction defined by the longitudinal axis L-L of the canister **5** (i.e. generally up and down when the device **1** is upright). The split-ring collar **33** permanently engages the container collar **30** to the canister **5** as described in U.S. patent application Nos. 10/110,611 (WO-A-01/28887) and US-A-2006/0082039.

[0149] The container collar **30** connects via closed coil extension springs **50a**, **50b** and respective spring connection points **31a**, **31b** and **41a**, **41b** to extension collar **40**, which is provided at its lower end with a ramp **44**. This multi-collar arrangement is

such that the extension collar **40** is moveable with respect to the container collar **30** along the longitudinal axis L-L of the drug discharge device.

[0150] The springs **50a**, **50b** will typically be formed of metal, for instance stainless steel, such as 302 grade stainless steel.

[0151] As shown in FIG. **5**, the extension collar **40** includes an actuating portion, in the form of shelf **42**, on opposing sides which are arranged for interaction with the lower ends **21a**, **21b** of the opposing levers **20a**, **20b** such that when the levers are squeezed together (i.e. inwards relative to the housing) the shelf **42** and hence, extension collar **40** are pushed downwards. The container collar **30** is further provided with flexible support legs **34a**, **34b** each of which is provided with a protruding foot **35a**, **35b** for latching engagement with a respective step **18a**, **18b** provided to the housing (see FIG. **2**). Each leg **34a**, **34b** also has a shaped head **36a**, **36b** the purpose of which will become clearer from the later description.

[0152] In the 'at rest' position of FIGS. **2** and **3a**, each foot **35a**, **35b** is slightly spaced from its respective step **18a**, **18b** on the housing. A third flexible support leg (not visible, but associated with third step **18c** as visible on FIG. **28**) locates at the rear of the container collar (i.e. there are three flexible support legs **34a**, **34b**). In one embodiment, the two support legs **34a**, **34b** on either side of the mouthpiece **14** are spaced at 113.4° intervals relative to a third support leg (not visible) which locates rearwards to the mouthpiece **14**.

[0153] The container collar **30** is further provided with downward protrusions **38a**, **38b**, the purpose of which will become clear from the later description.

[0154] In general operational terms, referring now also to FIG. **3a**, the opposing levers **20a**, **20b** are moveable transversely with respect to the longitudinal axis L-L of the drug discharge device to apply a force to the shelf **42** of the extension collar **40** to move the extension collar **40** downwards along that longitudinal axis (i.e. towards stem block **8** and mouthpiece **14**).

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[0155] The closed coil extension springs  $50a$ ,  $50b$  that connect the container collar  $30$  via connector points  $31a$ ,  $31b$  with the extension collar  $40$  act as a biasing mechanism to store biasing energy on moving the extension collar  $40$  downwards along the longitudinal axis L-L in response to squeezing of the levers  $20a$ ,  $20b$ . In embodiments, an initial biasing tension-inherent in the closed coil form thereof—is present in the closed coil extension springs  $50a$ ,  $50b$  even when in their ‘at rest’ state.

[0156] The flexible support legs  $34a$ ,  $34b$  act to provide a pre-load mechanism to prevent transfer of that biasing energy to the container collar  $30$  to move the canister  $5$  downwards along the longitudinal axis L-L to actuate the valve thereof (and hence, to fire the aerosolized drug dose) until a pre-determined threshold force is overcome.

[0157] Further details of the operation of the device  $1$  (which results from an effective user actuation thereof) may be appreciated by making reference to FIGS.  $3a$  to  $4c$ , in which for clarity only selected parts relevant to the particular stage of operation represented are labelled.

[0158] FIG.  $3a$  shows how the device  $1$  is configured in the ‘at rest’ position, in this instance also with the mouthpiece  $14$  covered by the mouthpiece cover  $16$ . The levers  $20a$ ,  $20b$  are splayed apart and catch retainers  $24a$ ,  $24b$  provided to an inner part of the protruding end  $23a$ ,  $23b$  of each respective lever  $20a$ ,  $20b$  locate close to ‘stop’ positions defined by notches  $15a$ ,  $15b$  provided to the top parts  $10a$ ,  $10b$  of the housing. The lower ends  $21a$ ,  $21b$  of each lever  $20a$ ,  $20b$  seat against the shelf  $42$  of the extension collar  $40$  but no force acts on the extension collar  $40$ . The closed coil extension springs  $50a$ ,  $50b$  are therefore in their ‘at rest’ state with no externally-applied (i.e. by lever  $20a$ ,  $20b$  actuation) biasing energy stored therein (but only any initial biasing tension—inherent in the closed coil form of the extension springs  $50a$ ,  $50b$ —present). Each foot  $35a$ ,  $35b$  of the flexible support legs  $34a$ ,  $34b$  is slightly spaced from its respective step  $18a$ ,  $18b$  on the housing.

[0159] In FIG.  $3b$ , the device is shown at a first early stage of operation, after removal of the mouthpiece cover  $16$  from the mouthpiece  $14$ , in which the levers  $20a$ ,  $20b$  have been squeezed very slightly together. The lower ends  $21a$ ,  $21b$  of each lever  $20a$ ,  $20b$  push slightly down on the shelf  $42$  of the extension collar  $40$  such that the extension collar  $40$  is moved slightly downwards. That downwards movement of the extension collar  $40$  is transferred via the extension springs  $50a$ ,  $50b$  to the container collar  $30$ , which also moves slightly downwards. Importantly, this downwards movement of the container collar  $30$  brings each foot  $35a$ ,  $35b$  of the flexible support legs  $34a$ ,  $34b$  into latching engagement with its respective step  $18a$ ,  $18b$  on the housing. As a result of this latching engagement, further downwards movement of the container collar  $30$  is impeded.

[0160] In FIG.  $4a$ , the device is shown at a second stage of operation, in which the levers  $20a$ ,  $20b$  have been squeezed further together. The lower ends  $21a$ ,  $21b$  of each lever  $20a$ ,  $20b$  push further down on the shelf  $42$  of the extension collar  $40$  such that the extension collar  $40$  is moved downwards. That downwards movement of the extension collar  $40$  however, cannot now be transferred via the extension springs  $50a$ ,  $50b$  to the container collar  $30$  because of the latching engagement of each foot  $35a$ ,  $35b$  of the flexible support legs  $34a$ ,  $34b$  with its respective step  $18a$ ,  $18b$  on the housing. That latching engagement impedes the downwards movement of the container collar  $30$ . The downwards movement of the

extension collar  $40$  therefore results in the extending of each closed coil extension spring  $50a$ ,  $50b$ , thereby resulting in biasing energy being stored in the now-extended springs  $50a$ ,  $50b$ .

[0161] In FIG.  $4b$ , the device is shown at a third stage of operation, in which the levers  $20a$ ,  $20b$  have been squeezed even further together. The lower ends  $21a$ ,  $21b$  of each lever  $20a$ ,  $20b$  push even further down on the shelf  $42$  of the extension collar

$40$  such that the extension collar  $40$  is moved even further downwards. That further downwards movement of the extension collar  $40$  still cannot now be transferred via the extension springs  $50a$ ,  $50b$  to the container collar  $30$  because of the latching engagement of each foot  $35a$ ,  $35b$  of the flexible support legs  $34a$ ,  $34b$  with its respective step  $18a$ ,  $18b$  on the housing. The further downwards movement of the extension collar  $40$  therefore results in further extension of each extension spring  $50a$ ,  $50b$ , thereby resulting in further biasing energy being stored in the now well-extended springs  $50a$ ,  $50b$ .

[0162] Further, in the position shown in FIG.  $4b$ , ramps  $44$  provided to the extension collar  $40$  respectively engage with the shaped heads  $36a$ ,  $36b$  of the flexible legs  $34a$ ,  $34b$  and act on the already-tensed flexible legs  $34a$ ,  $34b$  such that each foot thereof  $35a$ ,  $35b$  is at the point of becoming displaced from its respective step  $18a$ ,  $18b$ . In essence, the ramp  $44$  acts to ‘guide’ the displacement action. Thus, FIG.  $4b$  corresponds to the position at which the pre-load threshold force (typically about 16N) provided by the latching engagement of the flexible legs  $34a$ ,  $34b$  with their steps  $18a$ ,  $18b$  is just about to be overcome by the biasing energy stored in the extension springs  $50a$ ,  $50b$ . This position therefore corresponds to the threshold (or ‘tipping point’) of the pre-load/stored biasing energy system defined by the components of the device. Applying any further squeeze force to the levers  $20a$ ,  $20b$  will result in that threshold being exceeded, and effective user actuation of the device  $1$ .

[0163] In FIG.  $4c$ , which corresponds to a fourth stage of operation, such further force has been applied to the levers  $20a$ ,  $20b$ . The protruding end  $23a$ ,  $23b$  (see also FIG.  $3a$ ) of each respective lever  $20a$ ,  $20b$  touches off one against the other, thereby

preventing any further lever  $20a$ ,  $20b$  travel. Most importantly, the flexible legs  $34a$ ,  $34b$  have become displaced from their respective steps  $18a$ ,  $18b$  through the action of the ramps  $44$ . The container collar  $30$  may now move freely downwards and indeed, will do so as a result of its experience of the biasing energy stored in the extension springs  $50a$ ,  $50b$ . The container collar  $30$  and canister  $5$  in permanent

engagement therewith move rapidly downwards propelled by the stored biasing energy of the springs  $50a$ ,  $50b$ . The valve of the canister  $5$  is thereby activated to release aerosolized drug through the passage  $9$  in the stem block  $8$  which guides that discharged aerosolized drug to the mouthpiece  $14$  for inhalation by the patient.

[0164] It will be appreciated that once the threshold force has been overcome (i.e. just past the ‘tipping point’ of the device) a uniform actuating force resulting from the energy stored in the springs  $50a$ ,  $50b$  is experienced by the container collar  $30$  and canister  $5$  regardless of how much extra force is applied by the patient to the levers  $20a$ ,  $20b$ . A consistent actuation of the valve of the canister  $5$  is thereby, enabled by the configuration of the device  $1$ .



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[0165] Following actuation, the coiled coil extension springs **50a**, **50b** return to their 'at rest' state (i.e. with no externally-applied biasing energy, but only any initial biasing tension inherent in the closed coil form of the extension springs **50a**, **50b** present). As will be appreciated by the skilled reader in the art, the return spring (not shown) of the valve of the valved canister provides energy to move the canister **5**, container collar **30**, extension collar **40** and levers **20a**, **20b** back to the 'at rest' position as shown in FIG. 2. Further actuating operations may therefore be conducted until the canister **5** is exhausted of its drug formulation contents.

[0166] FIG. 6 shows a particular detail of the first drug dispenser device of FIGS. 1 to 5. For succinctness, only those parts relevant to this detail are now described further.

[0167] As previously described, the container collar **30** is provided at its underside with two downward protrusions **38a**, **38b**. The mouthpiece cover **16** is further provided with P-shaped cam interference elements **17a**, **17b** joined together by bridge element **18**

and joining to the mouthpiece cover **16** by means of living hinge **19** about which the bridged interference elements **17a**, **17b** may pivot. When, as shown in FIG. 6, the mouthpiece cover **16** engages with the body **12** of the dispenser device **1** to close the mouthpiece **14** (i.e. in the mouthpiece-closed position) the interference elements **17a**, **17b** adopt a position in which they locate underneath the downward protrusions **38a**, **38b** in close proximity or abutment therewith to thereby prevent any downward movement of the container collar **30**. See also FIG. 3a. Unintended movement of the container collar **30** and hence, unintended actuation of the dispenser device **1** is hence prevented.

[0168] In a subtle point, it is noted that when the mouthpiece cover **16** is in place such that the interference elements **17a**, **17b** prevent the downward movement of the container collar **30** the levers **20a**, **20b**; extension springs **50a**, **50b**; and extension collar **40** are not locked and are therefore free to move. The levers **20a**, **20b** may thus, still be compressed to the point at which their protruding ends **23a**, **23b** touch off, but without any movement of the container collar **30** and actuation of the dispenser device **1**. When the protruding ends **23a**, **23b** are so touched off the user will also not be able to apply further, potentially damaging, force to the interference elements **17a**, **17b** or to the stem block **8**.

[0169] The relative positioning of the interference elements **17a**, **17b** and the collar protrusions **38a**, **38b** in the various stages of operation of the device **1** is shown in FIGS. 3 and 4. FIG. 3a shows the spatial relationship when the mouthpiece cover **16** is in the mouthpiece-closed position, whilst FIGS. 3b and 4a-4c show the spatial relationship with the cover **16** removed and the levers being depressed inwardly to fire the device **1**.

[0170] The mouthpiece cover **16** may take one of the particular forms described in PCT Patent Application No. WO-A-2007/028992, which claims priority from UK patent application No. 0 518 355 filed 8 Sep. 2005, the entire content of which applications, and any subsequent US (PCT) patent application, are incorporated herein by reference.

[0171] FIGS. 7 to 10 illustrate aspects of the air flow into and through the housing of the drug dispenser device of FIG. 1 during use thereof. For succinctness, only those parts of the drug dispenser relevant to these aspects are now described.

[0172] FIG. 7 shows the drug dispenser device **1** of FIG. 1 in a 'ready to use' position with the mouthpiece cover **16**

removed from the mouthpiece **14**. It will be noted that in this position, the mouthpiece cover **16** is pivoted to a position underneath the lower housing part **12**. The opposing levers **20a**, **20b**, which protrude from apertures **11a**, **11b** provided to the front **10a** and rear **10b** upper housing parts, are in their rest

position. It will also be noted that in this position, the opposing levers **20a**, **20b** act to block off the apertures **11a**, **11b** such as to prevent ingress of dirt particles or other debris into the body of the device **1**.

[0173] FIG. 8 shows the drug dispenser device **1** of FIG. 1 in the 'in use' position, in which the opposing levers **20a**, **20b** have been moved towards each other, typically in response to a patient finger and thumb squeezing action. In this position, the opposing levers **20a**, **20b** no longer act to block off the apertures **11a**, **11b** such that air **60a**, **60b** may flow through the opened up apertures **11a**, **11b** into the upper housing part **10a**; **10b** in response to patient inhalation **61** through the mouthpiece **14**.

[0174] The air flow 'in use' through the device **1** is now described in more detail with reference to FIGS. 9 and 10.

[0175] FIG. 9 shows one half of the device **1** of FIG. 1 in the 'in use' position, in which the mouthpiece **14** is revealed, and in which lever **20b** has been pushed inwards to open up aperture **11b**. External air **60b** may thus, now be drawn into the body of the device housing through this aperture **11b** (and also similarly through aperture **11a** on the other side) in response to patient inhalation through the mouthpiece **14**. In other words, the patient coordinates their inhalation at the mouthpiece **14** to depression of the levers **20a**, **20b** so that the resulting airflow through the housing **10a**, **10b**, which enters via the opened apertures **11a**, **11b** and exits through the mouthpiece **14**, is coincident with the release of the drug from the canister **5** caused through actuation of the levers **20a**, **20b**. The airflow thus entrains the drug into the respiratory tract of the patient.

[0176] FIG. 10 illustrates in more detail, the air flow **60a**, **62** through the body of the device **1** during use thereof (i.e. again with the device **1** in the 'in use' position of FIGS. 8 and 9).

[0177] Referring to FIG. 10 in more detail, the device **1** may be seen to comprise a discharge assembly in the form of a stem block assembly **3** which is integrally formed with the lower body part **12** and provides for the delivery of an aerosol spray of a drug on actuation of the inhaler. Mouthpiece **14** is a separately formed part which is fitted to the lower body part **12** (as shown in FIG. 28) and in use is gripped in the lips of the user to facilitate oral inhalation. Received within the an enclosed chamber defined by the housing parts **10a**, **10b**, **12** there is provided aerosol canister **5** which contains drug to be delivered on actuation of the inhaler and is fitted in the main body and fluidly connected to the stem block assembly **3**.

[0178] The mouthpiece **14** comprises an external section **15** which is configured to be gripped in the lips of a subject and defines a substantially cylindrical, open forward end through which an aerosol spray of a drug is in use delivered on actuation of the inhaler, an essentially 'bucket-shaped' open chamber form internal section **17** which has a closed rear section (other than air holes **66** and spray orifice **72** described hereinafter), and a discharge outlet in the form of a nozzle outlet **70** which is coupled to a rear end of the internal section **17**, such as to provide for the delivery of an aerosol spray **64** into and through the internal section **17**.

[0179] In response to patient inhalation, air **60a** is drawn down the rear part **10b** of the body of the device **1** past around

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the stem block assembly 3 and towards the rear of the internal section 17 of the mouthpiece 14, which is provided with a duality of slot-like air holes 66 at the rear (i.e. base of the 'bucket') thereof arranged about spray orifice 72. The air holes 66 may be equi-spaced from the spray orifice 72. As may be seen, when the air 60a is drawn through these dual air holes 66 a duality of air flows 62 is defined within the mouthpiece 14. This provides for a partly annular air flow at the inner peripheral surface of the mouthpiece 14, which partly sheaths the aerosol spray 64 as delivered from the spray orifice 72 of the nozzle outlet 70, thereby partly entraining the aerosol spray 64 and reducing deposition at the internal surface of the mouthpiece 14.

[0180] In this embodiment the rear of the internal section 17 has a generally flat shape, which forms the base of the 'bucket'. The edges of the base curve outwards such that the internal section 17 has an increasing internal dimension in a direction away from the stem block assembly 3.

[0181] The nozzle outlet 70 includes the spray orifice 72 which provides for the delivery of an aerosol spray through the internal section 17 of the mouthpiece 14 and a delivery channel 74 which fluidly connects the delivery passage 9 of the stem block assembly 3 to the spray orifice 72.

[0182] In this embodiment the delivery channel 74 is a tapering channel which narrows towards the spray orifice 74. In this embodiment the delivery channel 74 has straight wall sections.

[0183] In this embodiment, the stem block assembly 3 comprises the stem block 8 for receiving the valve stem 7 of the canister 5, and the nozzle outlet 70 of the mouthpiece 14 which is fluidly connected to the stem block 8, such as to provide for the delivery of an aerosol spray through the mouthpiece 14. The stem block 8 may be integrally formed with the lower body part 12.

[0184] The stem block 8 includes a tubular bore 76 for receiving the valve stem 7 of the canister 5, which in this embodiment is co-axial with the longitudinal axis H-H of the housing (FIG. 3a), which housing axis H-H in this embodiment is coincident with the longitudinal axis L-L of the drug delivery device when mounted in the drug dispenser device 1. The tubular bore 76 is open at one, the upper, end thereof and includes an upper section 77 which has an internal dimension which is substantially the same as the outer dimension of the valve stem 7 of the canister 5 and a lower section 78 which has a smaller dimension, which sections 77, 78 together define an annular seat for the distal end of the valve stem 7.

[0185] In this embodiment, the stem block 8 includes a lateral cavity 80 which slidably receives the nozzle outlet 70 of the mouthpiece 14 and is fluidly connected to the tubular bore 76 thereof. The nozzle outlet 70 is configured to be a tight friction fit in the lateral cavity 80 in the stem block 8. Desirably, the tight friction fit provides a gas-tight seal. In other embodiments, other types of sealing method, also preferably arranged to provide a gas-tight seal, may be employed.

[0186] With this configuration of the stem block assembly 3, the nozzle outlet 70 (or the mouthpiece 14) and the stem block 8 (or the lower housing part 12) can be formed of different materials and to different specifications which are specifically suited to their purposes.

[0187] FIG. 11 shows a variation 101 of the drug dispenser device of FIGS. 1 to 10, with like features being identified with like reference numerals. The device 101 of FIG.

11 is identical to the embodiment of FIGS. 1 to 10 in all aspects other than that the dual horizontal slot-like air holes

66 visible in FIG. 10 are replaced by an arrangement of four circular air holes 166 (only three visible in FIG. 11) about the spray orifice 172 at the rear (i.e. base of the 'bucket') of the internal section 117 of the mouthpiece 114. It may be seen that the four air holes 166 are arranged in a

generally circular arrangement about the spray orifice 172, in this embodiment being at 90° angular displacement relative to each other. The spray orifice 172 may be centrally located in the circular arrangement of the air holes 166. As may be seen in FIG. 11, when external air 160a is drawn through these plural spaced air holes 166 a plurality of air flows 162 is defined within the mouthpiece 114. This provides for an essentially annular air flow at the inner peripheral surface of the mouthpiece 114, which essentially sheaths the aerosol spray 164 as delivered from the spray orifice 172 of the nozzle outlet 170, thereby entraining the aerosol spray and reducing deposition at the internal surface of the mouthpiece 114.

[0188] FIGS. 30a to 30n show other mouthpiece forms 514a to 514n, which may be employed in the drug dispenser device of FIGS. 1 and 11 as an alternative to the

mouthpieces 14, 114 thereof. These alternative mouthpiece forms 514a to 514n differ only in the size, shape and number of respective air holes 566a to 566n provided to the rear of the internal section 517a to 517n of these alternative mouthpiece forms 514a to 514n, which air holes 566a to 566n are as before, arranged about a spray orifice 572a to 572n.

[0189] Thus, FIGS. 30a to 30d and 30i show different arrangements of four circular air holes 566a to 566d and 566i; FIGS. 30e and 30f show different arrangements of three slot-like air holes 566e, 566f; FIGS. 30g and 30h show different arrangements of six slot-like air holes 566g, 566h; FIG. 30j shows an arrangement of many circular air holes 566j; FIG. 30k shows an arrangement of six curved slot air holes 566k arranged in two concentric rings; FIGS. 30l to 30n show different arrangements of three curved slot air holes 566l to 566n arranged in a ring pattern.

[0190] The upper front part 10a of the drug dispenser device 1, 101 of FIGS. 1 and 11 is arranged for receipt and housing of an actuation counter. FIGS. 12 to 18b provide details of the workings of a suitable actuation counter. FIGS. 19 to 21 show more details of the interaction of the actuation counter with the actuating mechanism of the drug dispenser device 1, 101.

[0191] Referring now to FIG. 12, this shows an actuation counter 201 for use with the drug dispenser device 1, 101 herein. FIGS. 13a and 13b respectively show underside and top views of the actuation counter 201.

[0192] The actuation counter 201 is comprised within upper front part 10a of the drug dispenser device 1 (or 101) provided with first 212 and second 214 spindle mountings, each capable of defining an axis of rotation and a circumferential wall 218 defining a bezel form retainer 219. A viewing window 216 is provided to the housing to enable the viewing of the count. As will be understood by a comparison of FIG. 1 with FIG. 13b, the oval-shaped front face 101 of the upper front part 10a is covered with a correspondingly shaped label 103 to cover the apertures in the

front face 101 shown in FIG. 13b, but not the viewing window 216. In other words, the label has an aperture 105 which registers with the viewing window 216. In an alternative embodiment, the label 103 may itself have a transparent portion in place of the aperture 105 to enable observation of the viewing window 216.

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[0193] Now describing the workings of the actuation counter in more detail: First, disc-shaped count wheel **220** has 'units' (i.e. numerals) count indicia **222** provided at spaced intervals on a top face thereof. The first count wheel **220** is provided with a central aperture **226** and a circular cavity **223** that is arranged for disposed receipt of ratchet wheel **250**. Ratchet drive receipt teeth **224** are arranged about the inner circumferential wall **225** of the cavity for ratcheted drive interaction with the ratchet wheel. **250**. The ratchet wheel **250** itself, is sized and shaped for receipt by the circular cavity **223** of the first count wheel and is provided with two oppositely-located drive tongues **252a**, **252b** for ratcheted drive interaction with the ratchet drive receipt teeth **224**. The ratchet wheel **250** is also provided with a drive-receiving protrusion **254** arranged in use, for drivable rotation of the ratchet wheel **250**. As will be described in more detail hereinafter with reference to FIGS. **19** to **21**, the drive-receiving protrusion **254** receives drive in response to drive interaction with downward drive slot **82** provided to front plate **80** in which the drive-receiving protrusion **254** is located. The front plate **80** is permanently fixed to the container collar **30** so as to move in tandem therewith. In this embodiment, the front plate **80** is permanently fixed to the container collar **30** by ultrasonic welding.

[0194] Noting that the front plate **80** moves on a linear path (along axis L-L) on actuation of the drug dispenser device **1**, **101** and that the ratchet wheel **250** rotates, the drive slot **82** allows for the transverse component of motion of the drive-receiving protrusion **254** therein as the ratchet wheel **250** rotates upon the drive-receiving protrusion **254** being driven by the drive slot **82**.

[0195] Second, ring form count wheel **230** also has 'tens of units' (i.e. decimals) count indicia **232** provided at spaced intervals on a top face **237** thereof and a set of teeth **234** provided in annular arrangement to the underside thereof. It may be noted that at stop position **238**, a couple of the teeth **234** have been removed and further that the outer circumferential edge of top face **237** is formed with a series of equally spaced notches or indentations **236**. The reasons for these features will become clear from the later description. The second count wheel **230** is also provided with a protruding shutter **280**, the function of which will also be described later.

[0196] Kick wheel **240** has kick teeth **244** provided in annular arrangement around the circumference thereof.

[0197] As may be best seen at FIG. **13a**, when assembled, second count wheel **230** is received for rotation within the bezel form retainer **219** of the housing; and first count wheel **220** is received within the inner ring void **235** defined by ring-shaped second count wheel **230** and its central aperture **226** by first spindle **212** such that clearance exists between the first **220** and second **230** count wheels. Thus, the first **220** and second **230** count wheels are in concentric relationship, but the level of the second count wheel **230** is slightly raised relative to that of the first count wheel **220** to enable shutter **280** to protrude over and above the first count wheel **220**. Ratchet wheel **250** is received within the circular cavity **223** of the first count wheel **220** such that drive tongues **252a**, **252b** engage with the ratchet drive receipt teeth **224**. Both wheels **220**, **230** and the ratchet wheel **250** are rotatable about a common first axis of rotation F-F defined in combination by the axis of first spindle **212** and the circular shape of the bezel retainer **219**. The drive-receiving protrusion **254** is offset from the first axis F-F, as is the drive slot **82**. Moreover, the protrusion **254** and drive slot **82** are both offset to the longitudinal axis L-L.

[0198] Kick wheel **240** is received by second spindle **214** for rotation about a second axis of rotation S-S defined by the second spindle **214** and therefore offset from the first axis of rotation F-F. It will be appreciated that the second axis of rotation S-S is spaced from the first axis of rotation F-F to be outside the path of rotation defined by the

outwardly-facing teeth **234** of the second count wheel **230**. Moreover, the first and second axes F-F, S-S are parallel, or substantially parallel, to each other.

[0199] The set of kick teeth **244** of the kick wheel **240** are in meshed relationship with the set of teeth **234** of the second count wheel **230** such that rotary motion of the kick wheel **240** results in rotary motion of the second count wheel **230**. In turn, ratchet drive tongues **252a**, **252b** of ratchet wheel **250** mesh with the ratchet drive receipt teeth **224** of the first count wheel **220** for drivable rotation of the first count wheel **220**.

[0200] As will be described in more detail hereinafter, when the actuation counter **201** is disposed in the drug dispenser **1**, **101**, the ratchet wheel **250** is in turn drivably rotatable about the first axis F-F by the drive-receiving interaction of protrusion **254** with downward drive slot **82** provided to front plate **80**. The front plate **80** fixes to the container collar **30**, which is itself drivable downwards in response to effective user actuation of the drug dispenser device **1**, **101**.

[0201] First count wheel **220** may also be seen to be provided at its periphery with a pair of fixed index teeth **228a**, **228b** (as may be best seen in FIG. **15a**) arranged for intermittent meshing with the kick teeth **244** of the kick wheel **240** such that rotary motion of the kick wheel **240** results from rotary motion of the first count wheel **220** only when said intermittent meshing occurs.

[0202] In a subtle aspect, it may be seen that the profile of all teeth **234**, **228a**, **228b**, **244** has a flanged form, which is selected to optimise the various toothed engagements necessary for effective gearing and inter-operability of the parts of the counter.

[0203] In a further subtle aspect, the counter **201** is arranged to count down from '120' to a 'shuttered position'. The second count wheel **230** is thus, arranged to define fourteen equal pitches allied to twenty-six (calculated as  $(2 \times 14) - 2$ ) teeth **234** plus two missing teeth at stop position **238**. The number of pitches is defined as  $x+2$ ,

wherein  $x$  is the highest numeral on the second count (i.e. decimals) wheel, which in turn corresponds to a highest count of 10 times  $x$  (i.e.  $10 \times 12 = 120$ , in this embodiment). The '+2' part of the sum determining the number of pitches relates to one coloured portion **282** and one shutter portion **280**, as are described in more detail later.

[0204] Overall, it may be noted that the actuation counter **201** has a relatively compact form to assist its receipt within the upper front housing part **10a** of the drug dispenser device **1**, **101**. In particular, the counter **201** extends upwards in the direction of the axes F-F, S-S to only a minor extent.

[0205] Operation of the actuation counter **201** is now described with additional reference to FIGS. **14a** to **16b**, in which only the most relevant features to the described operation are labelled. The actuation counter **201** is arranged to count down and thus, to illustrate a count operation, FIGS. **14a**, **15a** and **16a** show the actuation counter **201** at a 'count 120' position and FIGS. **14b**, **15b** and **16b** show the actuation counter **201** at a 'count 119' position (i.e. just after counting down from 120).



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[0206] It will be appreciated that the 'count' of the dose counter 201 referred to herein is the count number collectively presented by the count wheels 220, 230 in the window 216.

[0207] To initiate a general count operation, ratchet wheel 250 is rotated in response to effective user actuation of the drug dispenser device 1, 101 by squeezing the levers 20a, 20b together as described with reference to FIGS. 1 to 7 above. This results in the drive slot 82 driving the ratchet wheel protrusion 254 to rotate the ratchet wheel 250 in a first rotary sense (clockwise in FIGS. 12 and 13a).

[0208] This, in turn, results in rotation of the first count wheel 220 in the first rotary sense by the meshed interaction of drive tongues 252a, 252b with ratchet drive receipt teeth 224. The ratchet wheel 250 and first count wheel 220 are configured and arranged such that

when indexed first count wheel 220 rotates by 36° such that a single indicium 222 thereon is advanced (i.e. the 'units' count moves down one unit).

[0209] Where the pre-count operation visible count is x0 (e.g. 120 with 'x=12', as shown at FIGS. 14a, 15a and 16a), the counting action resulting from the use operation is subtly different. Once again, ratchet wheel 250 is rotated in response to effective user actuation of the drug dispenser device 1, 101 causing rotation of the first count wheel 220 by 36° such that the 'unit'

indiciu 222 moves on from '0' to '9' (as shown at FIGS. 14b and 15b). This rotation of the first count wheel 220 however, also brings the pair of index teeth 228a, 228b into meshed relationship with the kick teeth 244 of kick wheel 240 such that the kick wheel 240 rotates and in turn, causes the second count wheel 230 to rotate through meshing of their respective teeth 234, 244. The wheels 220, 230, 240 are configured and arranged such that the resultant rotation of the second count wheel 230 is by 360/14° (that is to say by 360/n° wherein n is the number of number spacings, where in this case n=14 because there are twelve decimals indicia 232; one shutter portion 280 and one coloured portion 282) such that a single indicium 232 thereon is advanced (i.e. the 'tens' count moves down exactly one unit). In this instance, the decimal indicium 232 moves down from '12' to '11', as shown in FIGS. 14a and 14b.

[0210] Where the previous visible count was 10 (i.e. x=1), the counting action resulting from the use operation is again subtly different in that the kick wheel 240 action, as described above, results in the coloured (e.g. red) portion 282 of the second count wheel 230 being advanced into place in the window 216 such that the next display is 'red 9' (i.e. coloured portion 282; and numerals indicia 222 is number 9).

[0211] As shown at FIGS. 17a and 18a, where the previous visible count was 'red 0' (i.e. X=0), the counting action resulting from the use operation is still again subtly different in that the kick wheel 240 action, as described above, results in the shutter portion 280 of the second count wheel 230 being advanced into place in the window 216 such that the next display is fully shuttered off (i.e. no indicia 222, 232 visible at all,

as shown at FIGS. 17b and 18b). Additionally, the stop position 238 in the set of second count wheel teeth 234 is brought into opposed relation with the kick teeth 244 whereby the kick teeth 244 and the teeth 234 no longer mesh. Thus, if the first count wheel 220 continues to rotate, e.g. in response to continued user operation of the drug dispenser device 1, 101 into which the actuation counter 201 is incorporated, notwith-

standing that all drug doses in the prescribed dosing regime have been dispensed (although surplus doses may remain in the canister 5 for patient administration in accordance with regulatory requirements, as understood by the skilled person in the art), the index teeth 228a, 228b of the first count wheel 220 will still intermittently mesh with the kick teeth 244 to cause the kick wheel 240 to rotate. However, this rotation of the kick wheel 240 will not be transmitted to the second count wheel 230, due to the missing teeth of stop position 238, and the shutter 280 remains in the shuttering position in the window 216 so that the underlying 'units' indicium 222 remains unseen.

[0212] In this embodiment, the second count wheel 230 is integrally formed with the shutter portion 280.

[0213] To further illustrate the countdown display of the counter 201, the reader's attention is drawn to Table 1 below. Table 1 shows the sequential countdown for each of the units (first) and decimals (second) count wheels 220, 230 upon succeeding use operations or actuations of the counter 201, and also indicates which of these two count wheels 220, 230 indexes to bring the counter 201 to its new counter display.

[0214] As shown in Table 1, the first (units) count wheel 220 indexes on each counter actuation, whereas the second (decimals) count wheel 230 only indexes (through the kick wheel 240 supra) each time the units indicium 222 of the first (units) count wheel

220 in the window 216 decrements from '0' to '9'. At the end of the countdown, when the display is shuttered, the first count wheel 220 is still free to rotate, underneath the shutter 280 so as not to be visible, and no further indexing of the second count wheel 230 occurs due to the stop position 238 providing for disengagement of the teeth 234, 244 of the second count wheel 230 and the kick wheel 240.

TABLE 1

Sequential Decimals Units Wheel Indexing of Units Inde of Counter Wheel Count Count in Wheel to this Dec Wheel Display in in Window Window Count? toth
Window
120 12 0 - -
119 11 9 Yes Yes
118-110 11 8 to 0 Yes No
109 10 9 Yes Yes
108-100 10 8 to 0 Yes No
99 9 9 Yes Yes
98-90 9 8 to 0 Yes No
89 8 9 Yes Yes
88-80 8 8 to 0 Yes No
79 7 9 Yes Yes
78-70 7 8 to 0 Yes No
69 6 9 Yes Yes
68-60 6 8 to 0 Yes No
59 5 9 Yes Yes
58-50 5 8 to 0 Yes No
49 4 9 Yes Yes
48-40 4 8 to 0 Yes No
39 3 9 Yes Yes
38-30 3 8 to 0 Yes No
29 2 9 Yes Yes
28-20 2 8 to 0 Yes No
19 1 9 Yes Yes
18-10 1 8 to 0 Yes No
9 'Red' 9 Yes Yes
8-0 'Red' 8 to 0 Yes No
Shuttered Shuttered Shuttered Yes Yes

[0215] After effective user actuation of the drug dispenser device 1, 101 and registration of the count, the levers 20a, 20b

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are released to return to their outward rest position and to allow the container collar **30** to return to its rest position. This results in the ratchet wheel **250** reversing, to reset it in its starting position for the next counting event, through interaction of the drive slot **82** with the drive-receiving protrusion **254**.

[0216] Thus, the ratchet wheel **250** is adapted to not only rotate in the cavity **223** of the first count wheel **220** in the first rotary sense (clockwise as viewed in FIGS. **12** and **13a**), but also to rotate in an opposite, second rotary sense (anti-clockwise as viewed in FIGS. **12** and **13a**) in the first count wheel cavity **223**.

[0217] However, while rotation of the ratchet wheel **250** in the first rotary sense drivably rotates the first count wheel **220** in the first rotary sense for indexing of the units count **222** in the window **216**, rotation of the ratchet wheel **250** in the opposite, second rotary sense is relative to the first count wheel **220**; i.e. the first count wheel **220** remains stationary so that the units indicia **222** in the window **216** remains unchanged. That is to say, frictional engagement between the respective wheels **220**, **250** does not result in reverse rotation of the first count wheel **220**, except for tolerance adjustments as discussed below.

[0218] To this end, the first count wheel **220** is provided with a pair of diametrically opposed resilient tongues or pawls **227** which co-operate with a serrated circumferential surface **211** of the first spindle **212a**. The serrated surface **211** comprises plural **25** ratchet teeth **215** with which the free ends **227a** of the pawls **227** engage. As the skilled person will understand, as the first count wheel **220** is driven by the ratchet wheel **250** to rotate in the first sense, the free ends **227a** of the pawls **227** ride over the respective ratchet tooth **215** presently engaged with and drop onto the next adjacent ratchet tooth **215** in the first sense, there being a step between adjacent teeth **215**. This then indexes the first count wheel **220** in its new position, at which the next units indicia **222** in the count sequence registers with the window **216**. However, the step between the adjacent ratchet teeth **215** prevents the first count wheel **220** rotating back in the opposite, second sense as the ratchet wheel **250** so rotates as the pawl free ends **227a** cannot pass thereover.

[0219] As will also be appreciated by the skilled person, the ratchet teeth **215** provide tolerances in the indexing rotation of the first count wheel **220** by the ratchet wheel **250**. In other words, the first count wheel **220** can be slightly over-rotated in the first sense, but as the ratchet wheel **250** rotates back in the opposite, second sense it carries the first count wheel **220** in the same sense, through frictional forces, until the pawl free ends **227a** engage the step between the ratchet teeth **215** which then prevents further reverse rotation of the first count wheel **220** and indexes the units indicia **222** in the window **216**.

[0220] As shown in FIGS. **12** and **13b**, for example, the upper front part **210** of the drug dispenser device **1**, **201** further provides a resilient pawl **217**. The pawl **217** has a free end **217a** which engages the indentations **236** in the outer circumferential

surface of the top face **237** of the second count wheel **230**, as shown in FIGS. **14a** and **14b**, for instance. There is one indentation **236** for each count or index position of the second count wheel **230**, so the free end **217a** of the pawl **217** and the indentations **236** provide an indexing function which provides for accurate alignment of the decimals indicia **234** in the window **216** and inhibits or prevents reverse rotation of the second count wheel **230**.

[0221] The indentations **236** in this embodiment have a symmetrical shape, more particularly a generally U-shape. However, other shapes could be used. Moreover, asymmetric shapes could also be used. For instance, it may be useful for the flanks of the indentations **236** to present different angles, for example for the trailing (rear) flanks of the indentations **236** (relative to the direction of rotation of the second count wheel **230**, e.g. anti-clockwise in FIGS. **14a** and **14b**) to form a greater angle with a central radial line through the indentations **236** than the leading (forward) flanks. This means there is less resistance to the pawl **217** releasing from the indentations **236** as the second count wheel **230** is driven by the kick wheel **240**.

[0222] It will be appreciated that the above usage of the actuation counter has been described in terms of a counter assembly **201** arranged to count downwards (i.e. to count on from 'n+1' to 'n' on indexing), but that the counter assembly may be straightforwardly modified to count upwards (i.e. instead to count on from 'n' to 'n+1' on indexing).

[0223] The components of the actuation counter **201** and any assemblies and sub-assemblies described above may be made from any suitable materials such as plastic polymer materials (e.g. acetal or ABS or styrene polymers).

[0224] In a modification of the counter **201** (not shown), the friction resistance between the kick wheel **240** and its spindle mounting **214** may be increased to provide a dragging or braking effect which retards the speed of rotation of the kick wheel **240** when driven by the first count wheel **220**. One possible way to achieve this is through the provision of axially-oriented splines about the outer periphery of the spindle mounting

**214**. This may prevent or inhibit any tendency for the second count wheel **230** to be misaligned or over-indexed by a fast moving kick wheel **240**.

[0225] The interrelationship between the actuation counter **201** and the drug dispenser device **1** is now described in more detail with reference to FIGS. **19** to **21**. For clarity and succinctness, only relevant parts of FIGS. **19** to **21** are labelled.

[0226] FIGS. **19** shows the drug dispenser device **1** with upper front cover part **10a** and actuation counter **201** removed. The device **1** is in the 'at rest' position with the levers **20a**, **20b** not depressed.

[0227] FIG. **20** shows the drug dispenser device **1** with the upper front cover part **10a** and actuation counter **201** disposed therein shown detached from the remainder of the device **1**. The drug dispenser device **1** is again in the 'at rest' position with the levers **20a**, **20b** not depressed. FIG. **21** shows further details of the actuation counter **201** disposed in the upper front cover part **10a** of the drug dispenser device **1**.

[0228] Arrow A of FIG. **20** indicates the direction of movement of the container collar **30** and front plate **80** attached thereto resulting from effective user actuation of the drug dispenser device. Arrow B of FIG. **20** indicates the resulting interaction between the downward drive slot **82** of the front plate **80** and the drive-receiving protrusion **254** of the ratchet wheel **250** of the actuation counter **201**.

[0229] Detailed aspects of the drug dispenser device **1** and actuation counter **201** of FIGS. **19** to **21** correspond to those already described by reference to FIGS. **1** to **11** and FIGS. **12** to **18b** respectively, and for succinctness these are not described further.

[0230] Registration of a count is now described. In use, following effective user actuation of the drug dispenser

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device **1** by squeezing the levers **20a**, **20b** together, as described hereinabove with reference to FIGS. **1** to **7**, the container collar **30** and front plate **80** move downwards in tandem. The downward drive slot **82** on the front plate **80** drivably engages the drive-receiving protrusion **254** to drive on the ratchet wheel **250** of the actuation counter thereby resulting in registration of a count. As described previously, effective user actuation which results in the downward movement of the container collar **30** (and actuation of drug release from the canister **5**) occurs only once a pre-load threshold ('tipping') force has been overcome (by that effective user actuation). Thus, it will also be appreciated that a count is only registered by the actuation counter **201** in response to such an effective user actuation. The registered count thus, fully ties in with the number of occurrences of drug release.

[0231] FIGS. **22** to **27c** show different aspects of key parts of an alternative internal mechanism for use with the drug dispenser device **1** and canister **5** as hereinbefore

described. This alternative mechanism may be appreciated to be a slight variation of that previously described, mainly in relation to FIG. **5**.

[0232] Details of the container collar **330** of the alternative internal mechanism are shown at FIGS. **22** and **23**. Details of the extension collar **340** of the alternative internal mechanism are shown at FIGS. **24** and **25**. Assembly steps relating to the alternative internal mechanism are illustrated at FIGS. **26a** to **26c**, and key operational aspects at FIGS. **27a** to **27c**.

[0233] As before, the container collar **330** permanently engages via split-ring collar **333** with the neck **305a** of the canister **305** such that the so-engaged parts are moveable together relative to the housing in a direction defined by the longitudinal axis L-L of the canister **305** (i.e. generally up and down when the device **1** is upright). The split-ring collar **333** permanently engages the container collar **330** to the canister **305** as described in U.S. patent application Ser. Nos. 10/110,611 (WO-A-01/28887) and US-A-2006/0082039.

[0234] Again, as before the container collar **330** connects via closed coil extension springs **350a** (only one visible in FIG. **26c**) and respective spring, connection points **331a**, **331b** and **341a**, **341b** to extension collar **340**, which is provided at its lower end with an outer ramp **344**, and also with an inner ramp **343**. This multi-collar arrangement is such that the extension collar **340** is moveable with respect to the container collar **330** along the longitudinal axis L-L of the drug discharge device.

[0235] The extension collar **340** includes an actuating portion in the form of shelf **342**, which is arranged for interaction with the lower ends **21a**, **21b** of the opposing levers **20a**, **20b** such that when the levers **20a**, **20b** of the device **1** are squeezed together (i.e. inwards relative to the housing) the shelf **342** and hence, extension collar **340** are pushed downwards. The container collar **330** is further provided with flexible support legs **334a**, **334b**, **334c** which as before, act to provide a pre-load mechanism to prevent transfer of that biasing energy to the container collar **330** to move the canister **5** downwards along the longitudinal axis L-L to actuate the valve thereof

(and hence, to fire the aerosolized drug dose) until a pre-determined threshold force is overcome. Again, as before each flexible support leg **334a**, **334b**, **334c** is arranged for interaction with a respective step **18a**, **18b** on the housing. However, in this variation each flexible support leg **334a**, **334b**, **334c** is provided with a protruding inner foot **335a**,

**335b**, **335c** and protruding outer foot **336a**, **336b** (only two visible) the purpose of which will become clearer from the later description.

[0236] Assembly steps relating to those key parts of the alternative internal mechanism are illustrated at FIGS. **26a** to **26c**. The split-ring collar **333**, which generally comprises a plastic polymer material, is used to permanently fix the container collar **330** to the neck **305a** of the canister **305** by ultrasonic welding, as generally described in U.S. patent application Ser. Nos. 10/110,611 (WO-A-01/28887) and US-A-2006/0082039.

[0237] The welding process may use two sonotrodes (ultrasonic welding heads) each with three small conical projections to focus the weld energy. During the welding process the conical projections are plunged into the outer surface of the container collar **330** allowing the ultrasonic energy to create a pool of molten material to form the bond (welds) between inside surface of the container collar **330** and the outer surface of the split-ring collar **333**, which is wedged between the neck **305a** of the container **305** and the inside surface of the container collar **330**.

[0238] In a subtle variation of that ultrasonic welding process, the inner surface of the container collar **330** is provided with plural (e.g. two sets of three) spaced longitudinal ribs (not visible). During this variation of the welding process one or more plural pronged (e.g. three pronged) ultrasonic welding heads (not shown) are arranged about the container collar **330** with their prongs aligned one to each rib (which abut with the split-ring collar **333** which is wedged between the container neck **305a** and the ribs) and ultrasonic energy applied to form welds between the inside surface of the container collar **330** and the outside surface of the split-ring collar **333** using the rib material.

[0239] This alternative welding process, which is known as an 'energy deflection' method avoids any 'splash back' of particulate weld material which may otherwise occur where some of the molten material may be displaced onto the outside surface of the container collar **330** to form a 'splash' thereon which can subsequently detach. Such 'splash back' is disadvantageous because any particulates resulting therefrom may potentially lodge within the dispenser and thus, possibly be inhaled by the user. As the alternative process focuses the weld energy at the internal ribs, the sonotrode(s) no longer has the conical projections and, as the ribs are sandwiched between the container collar **330** and the split-ring collar **333**, most if not all extraneous molten material will be encapsulated and therefore unable (or less able) to become detached.

[0240] As shown at FIG. **26a**, in a first step of the assembly process, the canister **305** with split-ring collar **333** located about its neck **305a** is aligned above the container collar **330** and extension collar **340**. In a next step, as shown at FIG. **26b**, the canister **305** with split-ring collar **333** is inserted into the container collar **330**, the split-ring collar **333** is adjusted to be wedged between the neck **305a** and the inside surface of the container collar **330** and then the container collar **330** and the split-ring collar **333** are permanently joined by one of the afore-described welding processes to thereby

permanently fix the container collar **330** to the canister **305**. The so-engaged parts **305**, **330**, **333** are moveable together relative to the housing in a direction defined by the longitudinal axis L-L of the canister **305** (i.e. generally up and down when the device **1** is upright).



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[0241] The canister 305 and container collar 330 assembly is then inserted into the extension collar 340. The container collar 330 is connected via closed coil extension springs 350a (only one visible) and respective spring connection points 331a, 331b and 341a, 341b to the extension collar 340, as shown at FIG. 26c. When so-connected, the extension collar 340 is moveable with respect to the container collar 330 along the longitudinal axis L-L of the drug discharge device.

[0242] It will be appreciated that the overall form of the alternative internal mechanism is very similar to that previously described in relation to FIG. 5 other than that the shaping of the flexible support legs 334a, 334b, 334c differs slightly from those legs 34a, 34b of the internal mechanism of FIG. 5, and that correspondingly the ramp 44 thereof is replaced in the alternative internal mechanism by both an inner 343 and outer 344 ramp. The operational effect of these slight variations is described in greater detail below in relation to FIGS. 27a to 27c. Other than these slight variations, the general principles of operation of the device 1 with the alternative internal mechanism of FIGS. 22 to 27c correspond to those previously described with reference to FIGS. 3a to 4c.

[0243] Thus, in general operational terms, referring now also to FIGS. 27a to 27c, the opposing levers 20a, 20b of the device 1 are moveable transversely with respect to the longitudinal axis L-L of the drug discharge device to apply a force to the shelf 342 of the extension collar 340 to move the extension collar 340 downwards along that longitudinal axis (i.e. towards stem block 8 and mouthpiece 14 of the device 1).

[0244] The closed coil extension springs 350a that connect the container collar 330 via connector points 331a, 331b with the extension collar 340 act as a biasing mechanism to store biasing energy on moving the extension collar 340 downwards along the longitudinal axis L-L in response to squeezing of the levers 20a, 20b. In embodiments, an initial biasing tension—inherent in the closed coil form thereof—is present in the closed coil extension springs 350a even when in their ‘at rest’ state.

[0245] The flexible support legs 334a, 334b, 334c act to provide a pre-load mechanism to prevent transfer of that biasing energy to the container collar 330 to move the canister 305 downwards along the longitudinal axis L-L to actuate the valve thereof (and hence, to fire the aerosolized drug dose) until a pre-determined threshold force is overcome.

[0246] FIGS. 27a to 27c illustrate details of the relationship between a flexible support leg 334a of container collar 330 and an inner 343 and outer ramp 344 of the extension collar 340 during operation of the device 1.

[0247] FIG. 27a shows details of this relationship when the device 1 is in the ‘at rest’ position (i.e. corresponding to previous FIG. 3a). That is to say, with no downward force applied by the levers 20a, 20b to the shelf 342 of the extension collar 340. The flexible support leg 334a of the container collar 330 protrudes down between the inner 343 and outer 344 ramps of the extension collar 340, and interacts at its bottom end with a respective step 18a, 18b, 18c on the housing.

[0248] FIG. 27b shows details of this relationship when the device 1 is in a ‘tipping point’ configuration (i.e. roughly corresponding to previous FIG. 4c). In this position, significant downward force has been applied by the levers 20a, 20b of the device 1 to the shelf 342 of the extension collar 340. The outer ramp 344 of the extension collar 340 has been brought

down on the protruding outer foot 336a of the flexible leg support 334a, thereby causing the flexible leg support 334a to flex inwards and to be displaced interiorly to the outer ramp 344. In consequence, the container collar 330 may now move freely downwards and indeed, will do so as a result of its experience of biasing energy stored in the extension springs 350a. The container collar 330 and canister 305 in permanent engagement therewith move rapidly downwards propelled by the stored biasing energy of the springs 350a. The valve 306 of the canister 305 is thereby activated to release aerosolized drug for inhalation by the patient.

[0249] As before, it will be appreciated that once the threshold force has been overcome (i.e. just past the ‘tipping point’ of the device 1) a uniform actuating force resulting from the energy stored in the springs 350a is experienced by the container collar 330 and canister 305 regardless of how much extra force is applied by the patient to the levers 20a, 20b. A consistent actuation of the valve of the canister 305 is thereby enabled.

[0250] Following actuation, the coiled coil extension springs 350a return to their ‘at rest’ state (i.e. with no externally-applied biasing energy, but only any initial biasing tension inherent in the closed coil form of the extension springs 350a present). As will be appreciated by the skilled reader in the art, the return spring (not shown) of the valve 306 of the valved canister provides energy to move the canister 305, container collar 330, extension collar 340 and levers 20a, 20b back to the ‘at rest’ position. As shown at FIG. 27c, during this return operation the inner protruding foot 335a of the flexible leg 334a interacts with the inner ramp 343 of the extension collar 340, the effect of this interaction being to push the flexible leg 334a outwards to the ‘at rest’ state of FIG. 27a, in which the flexible leg 334a is un-flexed.

[0251] Where not stated, the components of the drug dispenser devices herein may be made from conventional engineering materials, especially conventional engineering plastics materials, more especially those which allow moulding of the component.

[0252] Each of the above-described embodiments may be modified to incorporate one or more features disclosed in the U.S. Provisional and/or International Applications incorporated herein by reference in the second and third paragraphs hereof.

[0253] It will be appreciated that the mouthpiece 14 in the exemplary embodiments could be configured instead as a nasal nozzle for insertion in a nostril of a human being, so that the drug formulation is deliverable to the nasal cavity of the human being.

[0254] The drug dispenser device herein is suitable for dispensing of a drug formulation to a patient. The drug formulation may take any suitable form and include other suitable ingredients such as diluents, solvents, carriers and propellants.

[0255] Administration of drug may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment or palliative care. It will be appreciated that the precise dose administered will depend on the age and

condition of the patient, the particular drug used and the frequency of administration and will ultimately be at the discretion of the attendant physician. Embodiments are envisaged in which combinations of drugs are employed.

[0256] Appropriate drugs may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergota-

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mine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (e.g. as the sodium salt), ketotifen or nedocromil (e.g. as the sodium salt); anti-infectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone (e.g. as the dipropionate ester), fluticasone (e.g. as the propionate ester), flunisolide, budesonide, rofleponide, mometasone e.g. as the furoate ester), ciclesonide, triamcinolone (e.g. as the acetonide) or  $6\alpha,9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo- $17\alpha$ -propionyloxy-androsta-1,4-diene- $17\beta$ -carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as free base or sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), salmefamol, carbutole, mabuterol, etaneterol, naminterol, clenbuterol, flerbuterol, bambuterol, indacaterol, formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, e.g. 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenylethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate);  $\alpha_4$  integrin inhibitors e.g. (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[[((2S)-4-methyl-2-{{[2-(2-methylphenoxy)acetyl]amino}pentanoyl}amino) propanoic acid (e.g. as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or

glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the drugs may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the drug.

**[0257]** The drug formulation may in embodiments, be a mono-therapy (i.e. single active drug containing) product or it may be a combination therapy (i.e. plural active drugs containing) product.

**[0258]** Suitable drugs or drug components of a combination therapy product are typically selected from the group consisting of anti-inflammatory agents (for example a corticosteroid or an NSAID), anticholinergic agents (for example, an  $M_1$ ,  $M_2$ ,  $M_{-1}/M_2$  or  $M_3$  receptor antagonist), other  $\beta_2$ -adrenoreceptor agonists, anti-infective agents (e.g. an antibiotic or an antiviral), and antihistamines. All suitable combinations are envisaged.

**[0259]** Suitable anti-inflammatory agents include corticosteroids and NSAIDs.

**[0260]** Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate,  $6\alpha,9\alpha$ -difluoro- $17\alpha$ -[(2-furanylcarbonyl)oxy]- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo-androsta-1,4-diene- $17\beta$ -carbothioic acid S-fluoromethyl ester,  $6\alpha,9\alpha$ -difluoro- $11\beta$ -

hydroxy- $16\alpha$ -methyl-3-oxo- $17\alpha$ -propionyloxy-androsta-1,4-diene- $17\beta$ -carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate,  $6\alpha,9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl- $17\alpha$ -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene- $17\beta$ -carbothioic acid S-fluoromethyl ester,  $6\alpha,9\alpha$ -difluoro- $17\alpha$ -[(2-furanylcarbonyl)oxy]- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo-androsta-1,4-diene- $17\beta$ -carbothioic acid S-fluoromethyl ester,  $6\alpha,9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl-3-oxo- $17\alpha$ -(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene- $17\beta$ -carbothioic acid S-cyanomethyl ester,  $6\alpha,9\alpha$ -difluoro- $11\beta$ -hydroxy- $16\alpha$ -methyl- $17\alpha$ -(1-methylcyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene- $17\beta$ -carbothioic acid S-fluoromethyl ester and  $9\alpha,21$ -dichloro- $11\beta,17\alpha$ -methyl-1,4-pregnadiene 3,20 dione-17-[2'] furoate (mometasone furoate).

**[0261]** Further corticosteroids are described in WO02/088167, WO02/100879, WO02/12265, WO02/12266, WO05/005451, WO05/005452, WO06/072599 and WO06/072600.

**[0262]** Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful are disclosed WO03/082827, WO98/54159, WO04/005229, WO04/009017,

WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899,

WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294,

WO04/026248, WO03/061651, WO03/08277, WO06/000401, WO06/000398 and WO06/015870.

**[0263]** Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukothene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists), inhibitors of cytokine synthesis or 5-lipoxygenase inhibitors. Examples of iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021, WO95/34534 and WO99/62875. Examples of CCR3 inhibitors include those disclosed in WO02/26722.

**[0264]** Suitable bronchodilators are  $\beta_2$ -adrenoreceptor agonists, including salmeterol (which may be a racemate or a single enantiomer, such as the R-enantiomer), for instance salmeterol xinafoate, salbutamol (which may be a racemate or a single enantiomer, such as the R-enantiomer), for instance salbutamol sulphate or as the free base, formoterol (which may be a racemate or a single diastereomer, such as the R,R-diastereomer), for instance formoterol fumarate or terbutaline and salts thereof. Other suitable  $\beta_2$ -adrenoreceptor agonists are 3-(4-{{[6-{{(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino]hexyl}oxy]butyl}benzenesulfonamide, 3-(3-{{[7-{{(2R)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl]phenyl]ethyl}amino]heptyl}oxy]propyl}benzenesulfonamide, 4-{{(1R)-2-[[6-{{2-[[2,6-dichlorobenzyl]oxy]ethoxy}hexyl]amino]-1-



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hydroxyethyl}-2-(hydroxymethyl)phenol, 4-[(1R)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol, N-[2-hydroxyl-5-[(1R)-1-hydroxy-2-[[2-4-[[[(2R)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide, and N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1/-)-quinolinon-5-yl)ethylamine, and 5-[(R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one. Preferably, the  $\beta_2$ -adrenoreceptor agonist is a long acting  $\beta_2$ -adrenoreceptor agonist (LABA), for example a compound which provides effective bronchodilation for about 12 hours or longer.

[0265] Other  $\beta_2$ -adrenoreceptor agonists include those described in WO 02/066422, WO

02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO 2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, WO 2004/039766, WO01/42193 and WO03/042160.

[0266] Preferred phosphodiesterase 4 (PDE4) inhibitors are cis 4-cyano-4-(3-cyclopentylloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol].

[0267] Other suitable drug compounds include: c/s-4-cyano-4-[3-(cyclopentylloxy)-4-methoxyphenyl]cyclohexan-1-carboxylic acid (also known as cilomast) disclosed in U.S. Pat. No. 5,552,438 and its salts, esters, pro-drugs or physical forms; AWD-12-5 281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (September 6-10, Edinburgh) 1998, Abst P. 98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO 99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L. J. et al. Eur Resp J [Annu Cong Eur Resp Soc (September 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a phthalazinohe (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4aR\*, 10bS\*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-5,8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vemalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585. 0

[0268] Further compounds are disclosed in WO04/024728, WO04/056823 and WO04/103998, all of Glaxo Group Limited.

[0269] Suitable anticholinergic agents are those compounds that act as antagonists at the 5 muscarinic receptor, in particular those compounds, which are antagonists of the M<sub>1</sub> or M<sub>3</sub> receptors, dual antagonists of the M<sub>1</sub>/M<sub>3</sub> or M<sub>2</sub>/M<sub>3</sub> receptors or pan-antagonists of the M<sub>1</sub>/M<sub>2</sub>/M<sub>3</sub> receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine,

homatropine, hyoscyamine; these compounds are normally administered as a salt, 0 being tertiary amines.

[0270] Other suitable anti-cholinergics are muscarinic antagonists, such as (3-enc/o)-3-(2,2-di-2-thienylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1] octane iodide, {3-endo)-3-(2-cyano<sup>-</sup>-diphenylethylO- $\delta,\delta$ -dimethyl- $\delta$ -azoniabicyclo[3.2.1] octane bromide, 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azonia bicyclo[2.2.2] octane bromide, (1R,5S)-3-(2-cyano-2,2-diphenylethyl)-6-methyl- $\delta$ -{2-[(phenylmethyl)oxy]ethyl}-8-azoniabicyclo[3.2.1] octane bromide, (eA<sup>?</sup>do)-3-(2-methoxy<sup>-</sup>-di-thiophen<sup>-</sup>yl-ethylO- $\delta,\delta$ -dimethyl- $\delta$ -azonia-bicyclo<sup>-</sup>.iloctane iodide, (endo)-3-(2-cyano-2,2-diphenyl-ethyl)- $\delta,\delta$ -dimethyl- $\delta$ -azonia-bicyclo[3.2.1]octane iodide, (endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)- $\delta,\delta$ -dimethyl- $\delta$ -azonia-bicyclo[3.2.1]octane iodide, (encfo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)- $\delta,\delta$ -dimethyl- $\delta$ -azonia-bicyclo[3.2.1]octane iodide, and (endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}- $\delta,\delta$ -dimethyl- $\delta$ -azonia-bicyclo[3.2.1] octane bromide.

[0271] Particularly suitable anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-43-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS-50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- $\delta$ O-50-2), clidinium bromide (Quarzan, CAS-34 $\delta$ 5-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71- $\delta$ 1- $\delta$ ), mepenzolate bromide (U.S. Pat. No. 2,91 $\delta$ ,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5 $\delta$ 70-29-1), tropicamide (CAS-150 $\delta$ -75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29 $\delta$ 68-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/0411 $\delta$ . Also of interest are revatropate (for example, as the hydrobromide, CAS 2625 $\delta$ 6-79- $\delta$ ) and LAS-34273 which is disclosed in WO01/0411 $\delta$ , darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name

Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

[0272] Other anticholinergic agents include compounds disclosed in U.S. Ser. No. 60/487,981 and U.S. Ser. No. 60/511,009.

[0273] Suitable antihistamines (also referred to as Hi-receptor antagonists) include any one or more of the numerous antagonists known which inhibit Hi-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with Hi-receptors. Examples include ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine.

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[0274] Examples of H1 antagonists include, without limitation, amlexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine, dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine, promethazine, terfenadine, tripeleminamine, temelastine, trimoprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine.

[0275] Exemplary H1 antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate. Ethylenediamines: pyrilamine maleate, tripeleminamine HCl, and tripeleminamine citrate.

Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine. Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H<sub>1</sub> receptor antagonist which may be used in combination with a PDE4 inhibitor.

[0276] The drug, or one of the drugs, may be an H<sub>3</sub> antagonist (and/or inverse agonist). Examples of H<sub>3</sub> antagonists include, for example, those compounds disclosed in WO2004/035556 and in WO2006/045416.

[0277] Other histamine receptor antagonists which may be used include antagonists (and/or inverse agonists) of the H<sub>4</sub> receptor, for example, the compounds disclosed in Jablonowski et al., J. Med. Chem. 46:3957-3960 (2003).

[0278] In embodiments, the drug formulation includes one or more of a  $\beta_2$ -adrenoreceptor agonist, a corticosteroid, a PDE-4 inhibitor and an anticholinergic.

[0279] Generally, powdered drug particles suitable for delivery to the bronchial or alveolar region of the lung have an aerodynamic diameter of less than 10 micrometers, preferably from 1-6 micrometers. Other sized particles may be used if delivery to other portions of the respiratory tract is desired, such as the nasal cavity, mouth or throat.

[0280] The amount of any particular drug or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The drugs for treatment of respiratory disorders herein may for example, be administered by inhalation at a dose of from 0.0008 mg to 10 mg, preferably 0.008 mg to 0.8 mg. The dose range for adult humans is generally from 0.0005 mg to 100 mg per day and preferably 0.01 mg to 1.5 mg per day.

[0281] In one embodiment, the drug is formulated as any suitable aerosol formulation, optionally containing other pharmaceutically acceptable additive components. In embodiments, the aerosol formulation comprises a suspension of a drug in a propellant. In embodiments, the propellant is a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

[0282] Suitable propellants include, for example, C<sub>n</sub> hydrogen-containing chlorofluorocarbons such as CH<sub>2</sub>ClF, CClF<sub>2</sub>CHClF, CF<sub>3</sub>CHClF, CHF<sub>2</sub>CClF<sub>2</sub>, CHClFCHF<sub>2</sub>,

CF<sub>3</sub>CH<sub>2</sub>Cl and CClF<sub>2</sub>CH<sub>3</sub>; C<sub>n</sub> hydrogen-containing fluorocarbons such as CHF<sub>2</sub>CHF<sub>2</sub>, CF<sub>3</sub>CH<sub>2</sub>F, CHF<sub>2</sub>CH<sub>3</sub> and CF<sub>3</sub>CHF<sub>2</sub>CF<sub>3</sub>; and perfluorocarbons such as CF<sub>3</sub>CF<sub>3</sub> and CF<sub>3</sub>CF<sub>2</sub>CF<sub>3</sub>.

[0283] Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above-identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chloro-fluorocarbons for example CHClF<sub>2</sub>, CH<sub>2</sub>F<sub>2</sub> and CF<sub>3</sub>CH<sub>3</sub>. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C<sub>n</sub> hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane (CF<sub>3</sub>CH<sub>2</sub>F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF<sub>3</sub>CHF<sub>2</sub>CF<sub>3</sub>) or mixtures thereof.

[0284] The drug formulations are preferably substantially free of chlorofluorocarbons such as CCl<sub>3</sub>F, CCl<sub>2</sub>F<sub>2</sub> and CF<sub>3</sub>CCl<sub>3</sub>. Preferably, the propellant is liquefied HFA134a or HFA-227 or mixtures thereof.

[0285] The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, liquefied, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations, which are free or substantially free of volatile adjuvants are preferred. In certain cases, it may be desirable to include appropriate amounts of water, which can be advantageous in modifying the dielectric properties of the propellant.

[0286] A polar co-solvent such as C<sub>2</sub>-6 aliphatic alcohols and polyols e.g. ethanol, isopropanol and propylene glycol, preferably ethanol, may be included in the drug formulation in the desired amount to improve the dispersion of the formulation, either as the only excipient or in addition to other excipients such as surfactants. In embodiments, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar co-solvent e.g. ethanol, preferably 0.1 to 5% w/w e.g. about 0.1 to 1% w/w. In embodiments herein, the solvent is added in sufficient quantities to solubilise part or all of the drug component, such formulations being commonly referred to as 'solution' aerosol drug formulations.

[0287] A surfactant may also be employed in the aerosol formulation. Examples of conventional surfactants are disclosed in EP-A-372,777. The amount of surfactant employed is desirable in the range 0.0001% to 50% weight to weight ratio relative to the drug, in particular, 0.05 to 10% weight to weight ratio.

[0288] The aerosol drug formulation desirably contains 0.005-10% w/w, preferably 0.005 to 5% w/w, especially 0.01 to 2% w/w, of drug relative to the total weight of the formulation.

[0289] In another embodiment, the drug is formulated as any suitable fluid formulation, particularly a solution (e.g. aqueous) formulation or a suspension formulation, optionally containing other pharmaceutically acceptable additive components.

[0290] Suitable formulations (e.g. solution or suspension) may be stabilised (e.g. using hydrochloric acid or sodium hydroxide) by appropriate selection of pH. Typically, the pH will be adjusted to between 4.5 and 7.5, preferably between 5.0 and 7.0, especially around 6 to 6.5.

[0291] Suitable formulations (e.g. solution or suspension) may comprise one or more excipients. By the term "excipient", herein, is meant substantially inert materials that are

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nontoxic and do not interact with other components of a composition in a deleterious manner including, but not limited to, pharmaceutical grades of carbohydrates, organic and inorganic salts, polymers, amino acids, phospholipids, wetting agents, emulsifiers, surfactants, poloxamers, pluronics, and ion exchange resins, and combinations thereof.

**[0292]** Suitable carbohydrates include monosaccharides include fructose; disaccharides, such as, but not limited to lactose, and combinations and derivatives thereof; polysaccharides, such as, but not limited to, cellulose and combinations and derivatives thereof; oligosaccharides, such as, but not limited to, dextrans, and combinations and derivatives thereof; polyols, such as but not limited to sorbitol, and combinations and derivatives thereof.

**[0293]** Suitable organic and inorganic salts include sodium or calcium phosphates, magnesium stearate, and combinations and derivatives thereof.

**[0294]** Suitable polymers include natural biodegradable protein polymers, including, but not limited to, gelatin and combinations and derivatives thereof; natural biodegradable polysaccharide polymers, including, but not limited to, chitin and starch, crosslinked starch and combinations and derivatives thereof; semisynthetic biodegradable polymers, including, but not limited to, derivatives of chitosan; and synthetic biodegradable polymers, including, but not limited to, polyethylene glycols (PEG), polylactic acid (PLA), synthetic polymers including but not limited to polyvinyl alcohol and combinations and derivatives thereof;

**[0295]** Suitable amino acids include non-polar amino acids, such as leucine and combinations and derivatives thereof. Suitable phospholipids include lecithins and combinations and derivatives thereof.

**[0296]** Suitable wetting agents, surfactants and/or emulsifiers include gum acacia, cholesterol, fatty acids including combinations and derivatives thereof. Suitable poloxamers and/or Pluronics include poloxamer 188, Pluronic® F-108, and combinations and derivations thereof. Suitable ion exchange resins include amberlite IR120 and combinations and derivatives thereof;

**[0297]** Suitable solution formulations may comprise a solubilising agent such as a surfactant. Suitable surfactants include  $\alpha$ -[4-(1,1,3,3-tetramethylbutyl)phenyl]- $\omega$ -hydroxy-poly(oxy-1,2-ethanediyl) polymers including those of the Triton series e.g. Triton X-100, Triton X-114 and Triton X-305 in which the X number is broadly indicative of the average number of ethoxy repeating units in the polymer (typically around 7-70, particularly around 7-30 especially around 7-10) and 4-(1,1,3,3-tetramethylbutyl)phenol polymers with formaldehyde and oxirane such as those having a relative molecular weight of 3500-5000 especially 4000-4700, particularly Tyloxapol. The surfactant is typically employed in a concentration of around 0.5-10%, preferably around 2-5% w/w based on weight of formulation.

**[0298]** Suitable solution formulations may also comprise hydroxyl containing organic co-solvating agents include glycols such as polyethylene glycols (e.g. PEG 200) and propylene glycol; sugars such as dextrose; and ethanol. Dextrose and polyethylene glycol (e.g. PEG 200) are preferred, particularly dextrose. Propylene glycol is preferably used in an amount of no more than 20%, especially no more than 10% and is most preferably avoided altogether. Ethanol is preferably avoided. The hydroxyl containing organic co-solvating

agents are typically employed at a concentration of 0.1-20% e.g. 0.5-10%, e.g. around 1-5% w/w based on weight of formulation.

**[0299]** Suitable solution formulations may also comprise solubilising agents such as polysorbate, glycerine, benzyl alcohol, polyoxyethylene castor oils derivatives, polyethylene glycol and polyoxyethylene alkyl ethers (e.g. Cremophors, Brij).

**[0300]** Suitable solution formulations may also comprise one or more of the following components: viscosity enhancing agents; preservatives; and isotonicity adjusting agents.

**[0301]** Suitable viscosity enhancing agents include carboxymethylcellulose, veegum, tragacanth, bentonite, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, poloxamers (e.g. poloxamer 407), polyethylene glycols, alginates xanthym gums, carageenans and carbopols.

**[0302]** Suitable preservatives include quaternary ammonium compounds (e.g. benzalkonium chloride, benzethonium chloride, cethmide and cetylpyridinium chloride), mercurial agents (e.g. phenylmercuric nitrate, phenylmercuric acetate and thimerosal), alcoholic agents (e.g. chlorobutanol, phenylethyl alcohol and benzyl alcohol), antibacterial esters (e.g. esters of para-hydroxybenzoic acid), chelating agents such as disodium edetate (EDTA) and other anti-microbial agents such as chlorhexidine, chlorocresol, sorbic acid and its salts and polymyxin.

**[0303]** Suitable isotonicity adjusting agents act such as to achieve isotonicity with body fluids (e.g. fluids of the nasal cavity), resulting in reduced levels of irritancy associated with many nasal formulations. Examples of suitable isotonicity adjusting agents are sodium chloride, dextrose and calcium chloride.

**[0304]** Suitable suspension formulations comprise an aqueous suspension of particulate drug and optionally suspending agents, preservatives, wetting agents or isotonicity adjusting agents.

**[0305]** Suitable suspending agents include carboxymethylcellulose, veegum, tragacanth, bentonite, methylcellulose and polyethylene glycols.

**[0306]** Suitable wetting agents function to wet the particles of drug to facilitate dispersion thereof in the aqueous phase of the composition. Examples of wetting agents that can be used are fatty alcohols, esters and ethers. Preferably, the wetting agent is a hydrophilic, non-ionic surfactant, most preferably polyoxyethylene (20) sorbitan monooleate (supplied as the branded product Polysorbate 80).

**[0307]** Suitable preservatives and isotonicity adjusting agents are as described above in relation to solution formulations.

**[0308]** The drug dispenser device herein is in one embodiment suitable for dispensing aerosolized drug (e.g. for inhalation via the mouth) for the treatment of respiratory disorders such as disorders of the lungs and bronchial tracts including asthma and chronic obstructive pulmonary disorder (COPD). In another embodiment, the invention is suitable for dispensing aerosolized drug (e.g. for inhalation via the mouth) for the treatment of a condition requiring treatment by the systemic circulation of drug, for example migraine, diabetes, pain relief e.g. inhaled morphine.

**[0309]** Administration of drug in aerosolized form may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will



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be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular particulate drug used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of drugs are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1, 2, 3 or 4 aerosol puffs each time. Each valve actuation, for example, may deliver 5  $\mu$ g, 50  $\mu$ g, 100  $\mu$ g, 200  $\mu$ g or 250  $\mu$ g of a drug. Typically, each filled canister for use in a metered dose inhaler contains 60, 100, 120 or 200 metered doses or puffs of drug; the dosage of each drug is either known or readily ascertainable by those skilled in the art.

[0310] In another embodiment, the drug dispenser device herein is suitable for dispensing fluid drug formulations for the treatment of inflammatory and/or allergic conditions of the nasal passages such as rhinitis e.g. seasonal and perennial rhinitis as well as other local inflammatory conditions such as asthma, COPD and dermatitis. A suitable dosing regime would be for the patient to inhale slowly through the nose subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril. Typically, one or two inhalations per nostril would be administered by the above procedure up to three times each day, ideally once daily. Each dose, for example, may deliver 5  $\mu$ g, 50  $\mu$ g, 100  $\mu$ g, 200  $\mu$ g or 250  $\mu$ g of active drug. The precise dosage is either known or readily ascertainable by those skilled in the art.

[0311] In another aspect, the drug dispenser device herein is suitable for dispensing fluid drug formulations for the treatment of inflammatory and/or allergic conditions of the nasal passages such as rhinitis e.g. seasonal and perennial rhinitis as well as other local inflammatory conditions such as asthma, COPD and dermatitis. A suitable dosing regime would be for the patient to inhale slowly through the nose subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied

to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril. Typically, one or two inhalations per nostril would be administered by the above procedure up to three times each day, ideally once daily. Each dose, for example, may deliver 5  $\mu$ g, 50  $\mu$ g, 100  $\mu$ g, 200  $\mu$ g or 250  $\mu$ g of active drug. The precise dosage is either known or readily ascertainable by those skilled in the art.

[0312] It will be understood that the present invention has been described above by way of example only and that the above description can be modified in many different ways without departing from the scope of the invention as defined by the appended claims.

[0313] All publications, patents, and patent applications cited herein, and any US patent family equivalent to any such patent or patent application, are hereby incorporated herein by reference to their entirety to the same extent as if each publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0314] It must be noted that, as used in the specification and appended claims, the singular forms "a", "an", "the" and "one" include plural referents unless the content clearly dictates otherwise.

What is claimed is:

1. A drug dispenser device for delivery of a drug by inhalation comprising

- (a) a housing defining a first chamber;
- (b) extending from said housing and defining a second open chamber, an outlet for insertion into a body cavity of a patient;
- (c) provided to said first chamber of the housing, a discharge block defining a discharge block orifice;
- (d) receivable within the first chamber for movement therein, a drug discharge device, said drug discharge device having a longitudinal axis and comprising a container for storing a drug formulation to be dispensed, a discharge mechanism and a discharge channel from said container, wherein said discharge channel is receivable by said discharge block to enable discharge of said drug formulation via said discharge block orifice to said outlet; and
- (e) provided to the housing, at least one finger operable member moveable to apply a force directly or indirectly to the drug discharge device for movement along the longitudinal axis towards the discharge block to actuate said discharge mechanism,

wherein said housing further defines an aperture through which said at least one finger operable member in part protrudes, and wherein the at least one finger operable member is moveable from a rest position in which the at least one finger operable member acts to block off said aperture to an actuating position in which the aperture is unblocked and through which air may be drawn into the housing in response to patient inhalation through the outlet.

2. A drug dispenser device according to claim 1, wherein the housing is sized and shaped to enable one-handed operation of the dispenser device.

3. A drug dispenser device according to claim 1, wherein the outlet is provided with a removeable protective cover.

4. A drug dispenser device according to claim 1, wherein the container has a cylindrical form and the longitudinal axis is defined by the central axis of the cylindrical container.

5. A drug dispenser device according to claim 1, wherein the discharge channel extends out from a neck of the container.

6. A drug dispenser device according to claim 1, wherein the outlet includes at least one air flow path which provides for a substantially annular air flow at an inner peripheral surface of the outlet on patient inhalation through the outlet, such as to provide a sheathing air flow thereat.

7. A drug dispenser device according to claim 6, wherein a circular arrangement of plural air flow paths is provided.

8. A drug dispenser device according to claim 1, wherein the discharge block comprises, as a separately-formed component, a discharge outlet which fluidly connects to the discharge block orifice of the discharge block and includes an discharge outlet orifice from which drug is in use delivered.

9. A drug dispenser device according to claim 8, wherein the discharge outlet is integrally formed with the outlet.

10. A drug dispenser device according to claim 8, wherein the discharge outlet is coupled to the outlet.

11. A drug dispenser device according to claim 8, wherein, the discharge block includes a laterally-directed cavity which receives the discharge outlet.

12. A drug dispenser device according to claim 11, wherein the discharge outlet is held captive in the laterally-directed cavity by means of a press-fit or snap-fit connection.

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13. A drug dispenser device according to claim 1, wherein at least a rear section of the discharge outlet has an increasing internal dimension in a direction away from the discharge block.

14. A drug dispenser device according to claim 13, wherein the discharge outlet defines an essentially cone-shaped interior.

15. A drug dispenser device according to claim 13, wherein the discharge outlet defines an essentially an essentially bucket-shaped interior.

16. A drug dispenser device according to claim 1, wherein the discharge outlet includes a delivery channel which fluidly connects to the discharge outlet orifice and narrows towards the same.

17. A drug dispenser device according to claim 16, wherein the delivery channel has arcuate wall sections.

18. A drug dispenser device according to claim 16, wherein the delivery channel has substantially straight wall sections.

19. A drug dispenser device according to claim 1, wherein the at least one finger operable member is moveable transversely with respect to the longitudinal axis of the drug discharge device.

20. A drug dispenser device according to claim 1, wherein the at least one finger operable member is arranged to apply mechanical advantage.

21. A drug dispenser device according to claim 20, wherein said mechanical advantage has a ratio of from 1.5:1 to 10:1.

22. A drug dispenser device according to claim 21, wherein the at least one finger operable member comprises a lever.

23. A drug dispenser device according to claim 22, wherein the at least one finger operable member comprises of at least one lever pivotally connected to part of the housing.

24. A drug dispenser device according to claim 23, wherein there are two opposing levers, each of which pivotally connects to part of the housing and arranged to urge the discharge device towards the discharge block when the two opposing levers are squeezed together by a user.

25. A drug dispenser device according to claim 24, wherein said two opposing levers are coupled to each other by a coupling mechanism.

26. A drug dispenser device according to claim 25, said coupling mechanism comprises meshing teeth provided to each of the two opposing levers.

27. A drug dispenser device according to claim 23, wherein the or each lever is pivotally supported at a lower end of the housing.

28. A drug dispenser device according to claim 1, wherein the at least one finger operable member is biased towards the rest position thereof.

29. A drug dispenser device according to claim 1, wherein in the actuating position a portion of the at least one finger

operable member engages the base of the container of the drug discharge device to push the container towards the discharge block in actuating fashion.

30. A drug dispenser device according to claim 1, wherein in the actuating position a portion of the at least one finger operable member engages an actuating mechanism capable of transferring force to the container of the drug discharge device to push or pull the container towards the discharge block in actuating fashion.

31. A drug dispenser device according to claim 30, additionally comprising

(f) connecting to the container, a container collar that engages the container;

(g) connecting to said container collar and moveable with respect thereto along the longitudinal axis of the drug discharge device, a transfer element, said transfer element including an actuating portion, wherein the at least one finger operable member is moveable to apply a force to said actuating portion of said transfer element to move the transfer element along the longitudinal axis in a first direction;

(h) connecting the container collar with the transfer element, a biasing mechanism to store biasing energy on moving the transfer element along the longitudinal axis in the first direction; and

(i) provided to the container collar, a pre-load mechanism to prevent transfer of said biasing energy to the container collar to move said container along the longitudinal axis in the first direction to actuate the discharge mechanism until a pre-determined threshold force is overcome.

32. A drug dispenser device according to claim 1, additionally comprising a locking mechanism for reversibly locking the movement of the at least one finger operable member.

33. A drug dispenser device according to claim 1, wherein the drug discharge device is suitable for discharging aerosolized drug and comprises an aerosol canister provided with a discharge valve having a valve stem.

34. A drug dispenser device according to claim 33, wherein the aerosol canister comprises an aerosol drug formulation comprising a drug in a propellant.

35. A drug dispenser device according to claim 34, wherein said propellant is a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

36. A drug dispenser device according to claim 1, wherein the drug is an anti-inflammatory agent.

37. A drug dispenser device according to claim 36, wherein said anti-inflammatory agent is selected from the group consisting of a corticosteroid, an NSAID, a glucocorticoid compound and mixtures thereof.

38. (canceled)

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